



Greater Manchester &
Cheshire Cancer Network

**Clinical Guidelines for the Management of Breast Disease including Breast Cancer
In the Greater Manchester & Cheshire Cancer Network**

(Peer Review Measures 11-1C-103b, 11-1C-105b, 11-1C-106b)

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SECTION 1

Foreword

In September 2000, the Government published The NHS Cancer Plan which set out the first ever comprehensive strategy to tackle cancer. The Cancer Plan identified a national cancer programme for England with four main aims:

- To save more lives
- To ensure people with cancer get the right professional support and care as well as the best treatments
- To tackle inequalities in health
- To build for the future through investment in the cancer workforce and strong research

In order to assist in implementing the aims of the Cancer Plan, 30 cancer networks have been established across England.

There are 3 Cancer Networks within the North West Region:

- _ Greater Manchester and Cheshire
- _ Merseyside and Cheshire
- _ Lancashire & South Cumbria

The Greater Manchester and Cheshire Cancer Network covers a population area of 3.2 million. Within this Network there are 12 acute trusts and 1 cancer centre:

- Bolton
- Central Manchester University Hospital (no local breast diagnostic or treatment service)
- Christie Hospital (no local breast diagnostic service, adjuvant treatment only)
- East Cheshire
- Mid Cheshire
- Pennine acute trust
- Salford Royal
- Stockport Foundation
- Tameside
- Trafford Health Care Trust (no local breast diagnostic or treatment service)
- University Hospital South Manchester
- Wrightington Wigan & Leigh

The Cancer Network ensures that health service commissioners (health authorities, primary care groups and trusts, GP Commissioners) and providers (primary and community care and hospitals), the voluntary sector and local authorities work together to establish and standardise clinical practices and deliver high quality care.

The Cancer Network Team are based at:

First Floor, Citibase Offices
40 Princess Street
Manchester M1 6DE
0161 920 9706

NHS Cancer Plan

Cancer Waiting Times Standards (2000 – 2008)

Target	Operational Standard
Maximum 2 weeks from urgent GP referral for suspected cancer to first outpatient attendance	93%
Maximum 2 weeks from referral of any patient with breast symptoms (where cancer not suspected) to first hospital assessment	93%
Maximum 31 days from decision to treat to first definitive treatment	96%
Maximum 31 days from decision to treat / earliest clinically appropriate date to start of second / subsequent treatment for all cancer patients including those diagnosed with a recurrence where the subsequent treatment is:	
a) Surgery	94%
b) Drug treatment	98%
c) radiotherapy	94%
Maximum 62 days from:	
1) urgent GP referral for suspected cancer to first treatment	85%
2) urgent referral from NHS Cancer Screening Programme (breast, cervical & bowel) for suspected cancer to first treatment	90%
3) consultant upgrade of urgency of referral to first treatment	TBC

Cancer Reform Strategy

Published in 2007, to build upon the cancer plan providing a clear direction for cancer services for the next 5 years. 10 areas were addressed, 6 to reduce cancer incidence and 4 to ensure delivery.

Recommendations pertaining to breast cancer include:

- Extend NHS BSP to 47-73 years, guaranteeing that every woman will have her first screening mammogram by age 50yrs, facilitated by the role of digital mammography
- Awareness programs to facilitate early diagnosis
- Evaluate delays in cancer diagnosis
- Fast access to best treatments
- 31 day standard to cover all cancer treatments
- 62 day standard to encompass all patients referred by GP with suspected cancer diagnosis and those diagnosed by screening
- Hospital specialists can promote patients to the 62 day standard if indicated, even if they have not been referred urgently by their GP
- All patients referred to a specialist with breast symptoms should be seen within 14 days
- To achieve a world class radiotherapy service, with all (not just the first) treatments within the 31 day standard. To implement the National Radiotherapy Action Group report ensuring that there is adequate capacity to meet this requirement.
- National Institute for Clinical Excellence appraisals to be carried out in parallel with drug licensing
- To understand why there are variations in chemotherapy drug usage; chemotherapy users will be required to return an approved data set
- Primary Care Trusts, working with others in the cancer network, to generate a strategic plan for cancer delivery
- To implement the National Chemotherapy Action Group report (2009)

- Improve information available to patients covering both the cancer and its management along with financial resource.
- Address survivorship issues
- Cancer care to be delivered locally whenever possible, however, centralization to occur to improve outcomes if necessary
- To shift to outpatient care when possible
- To enable GPs and hospital specialists rapid access to diagnostic tests
- To ensure equity of access
- National Cancer Intelligence service to collect defined data sets
- Stronger commissioning to drive service equality and value for money
- Cancer networks to support PCTs in their commissioning role, electronic commissioning tool kit
- Change to cancer payment to take account of a review of Payment by Results

NCEPOD (Confidential enquiry into patient outcomes and deaths)

- This report addressed patients who had died within 30 days of their last dose of chemotherapy.
- A number of recommendations were made:
- Hospital that deliver chemotherapy should have facilities to manage the acute complications of chemotherapy, or have formal agreement with another to provide that service
- Decision to treat, consent and performance status should be assessed by a sufficiently experienced clinician and should be in the patient's interests
- Systemic Anti-Cancer Treatment prescriptions should not be initiated by FY1, FY2, ST1 and ST2 grade doctors
- Doctors should modify dose following good clinical practice
- A local policy should exist for the management of neutropenic sepsis, staff should be appropriately trained, the policy should be available throughout the trust
- End of life care should be proactive
- All deaths within 30 days of chemotherapy should be considered at a morbidity and mortality meeting (clinical governance)

NICE and Breast Cancer

- The following guidance has been published by the National Institute for Clinical Excellence (NICE). This guidance is designed to cover most of the patients most of the time.
- They are not designed as a text book on breast cancer management and do not cover every eventuality.
- Topics covered are driven by the stakeholders.
- NICE confines itself to peer reviewed published data and is exclusive of abstracts and conference presentations. All guidance issued should be applied to each individual patient.
- NICE guidance is available at www.nice.org.uk/index
- Guidance is written in the following context, "This guidance represents the view of the institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement.
- The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the parent and or guardian or carer".

Service Guidance

- Improving Outcomes in Breast Cancer

August 2002

Update expected February 2012

Clinical Guidelines

- CG80 Breast Cancer (early & locally advanced): diagnosis and treatment February 2009
- CG81 Advanced Breast Cancer: NICE Guidance February 2009
- CG41 Familial Breast Cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (partial update of CG14) October 2006

Technology Appraisal

- TA107 Breast Cancer (early) – trastuzumab August 2006
- TA108 Breast Cancer (early) – paclitaxel September 2006
- TA109 Breast Cancer (early) – docetaxel September 2006
- TA112 Hormone therapies for adjuvant treatment or early oestrogen-receptor-positive breast cancer November 2006

Interventional procedures

- IPG147 Endoscopic axillary lymph node retrieval for breast cancer December 2005
- IPG156 Image guided vacuum assisted excision biopsy of benign breast lesions February 2006

Breast CSG Clinical Guidelines for the Management of Patients with Known or Suspected Breast Cancer

(Peer Review measure 11-1C-103b)

This document has been prepared by the working group set up by the GMCCN Breast CSG. It is a requirement of Peer Review and the Cancer Reform Strategy that all networks must have in place an agreed set of management procedures and guidelines to inform and shape high quality care of patients uniformly across each network.

The working group has met and recommends this provision of guidelines to be considered, finalised and endorsed by the Breast CSG. These guidelines have been formulated to inform those working across the network for patients with suspected or known breast cancer, and to lend support for those areas where investment of resource, personnel or process is needed. But primarily this document is to ensure that each patient within the network is treated within uniformly highest standards of care.

Patients with breast cancer are managed within the network at the Christie Hospital cancer centre, the associate cancer centres, university hospitals and other hospital trusts. A number of centres and units have already adopted their own guidelines and historically have worked to these. Some of these documents are lengthy, referenced and subject to regular updated review. Others are less formal, with broader strokes of detail, and not all are reviewed when the findings of clinical trials or the publication of new guidelines from NICE or a specialty association would indicate that revision should be done.

There is a standing working group of the GMCCN Breast CSG that will meet at least annually to consider such changes as may become necessary to be incorporated into these guidelines.

Multiple documents have been considered by the working group. These included formal, national, and in one case, other national published guidelines, endorsed by government organisations, specialist associations or both. Locally produced guidelines also were considered from individual hospitals.

In order to harmonise guidelines across the network, it was decided that with the exception of the Christie Breast Diagnosis Oriented Group (BDOG) cancer centre document, locally produced guidelines in individual hospitals should be subsumed by agreement to adopt national guidelines wherever possible when they already exist.

It is recognised that in many cases national guidelines themselves may leave out some details of aspects of care that as a network we would wish to be more prescriptive about. The role of a national document includes the need to set minimum standards that apply across the nation, whilst recognising that provision of resources and personnel may differ from one region to another. Nevertheless it is the case that national documents do set high standards that we must achieve for the benefit of our patients. Clearly it is essential any locally produced guidelines with which personnel are familiar, should be in agreement with, and not conflict with national guidelines. With that proviso, it is intended that wherever local guidelines add more detail to issues covered more broadly in the national guidelines, then the local guidelines may be continue to be referred to for patient care.

From the network cancer centre, the Christie BDOG guidelines direct practice. The working group accepts the role of these guidelines within the network, and looks to the Christie BDOG to disseminate the updated guidelines annually

In anticipation of the closer convergence of national breast cancer screening and symptomatic practices, the GMCCN Breast CSG adopts the following published guidelines.

The following guidelines are reviewed annually by the Breast CSG guidelines group and were last agreed by the Breast CSG members on 25 January 2012:

References:

NICE (2009). *“Early and locally advanced breast cancer: diagnosis and treatment.”*
National Cancer Action Team (NCAT) (2011) *“National Cancer Peer Review Programme. Manual for Cancer Services: Breast Measures. Version 2.0”*
Department of Health (2011) *“Improving Outcomes: A strategy for cancer.”*
Macmillan Cancer Support (2011) *“Psychological and emotional support provided by Macmillan Professionals: An evidence review.”*
Royal College of Nursing and Breast Cancer Care (2004) *“Time to care: Maintaining access to breast care nurses.”*
Barlow H et al (2011) *“The role of the clinical nurse specialist in cancer and specialist palliative care: sustaining the role into the future.”*

- **Breast Cancer Management Guidelines,**
Breast Disease Orientated Group, Christie Hospital, September 2011
- **Best Practice Diagnostic Guidelines for Patients Presenting with Breast symptoms**
Willet AM, Michell MJ, Lee MJR November 2010
- **Surgical guidelines for the management of breast cancer**
Association of Breast Surgery at BASO 2009,
Eur J Surg Oncol (2009) doi 10.1016/ejso.2009.01.008
- **Quality Assurance Guidelines for surgeons in breast cancer screening**
NHSBSP 2009, Department of Health Publications no. 20
- **Oncoplastic breast surgery – A guide to good practice**
Association of Breast Surgery at BASO, BAPRAS and the Training Interface Group in Breast Surgery 2007,
Eur J Surg Oncol 33 (2007) S1-S23
- **Breast cancer – early and locally advanced**
National Institute for Health and Clinical Excellence, 2009, NICE guideline 80
- **The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care**
National Institute for Health and Clinical Excellence, 2006, NICE guideline 41, update of 14

- **Quality assurance guidelines for nurses in breast cancer screening**
NHSBSP, 2008, Department of Health Publications no. 29
- **Quality assurance guidelines for mammography**
NHSBSP, 2006, Department of Health Publications no. 63
- **Quality assurance guidelines for breast cancer screening radiology**
NHSBSP 2005, Department of Health Publications no. 59
- **NHSBSP Guidelines for pathology reporting in breast cancer**
NHSBSP, 2005, Department of Health Publications no. 58
- **The management of metastatic bone disease in the United Kingdom**
1999, Eur J Surg Oncol 25 (1999) 3-23
- **European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition**
2009 Royal College of Radiologists and the European Commission

As a reference guide to support and inform practice, the National Comprehensive Cancer Network Clinical Guidelines in Oncology, Breast Cancer v.1.2009, is recommended for background reading. The comprehensive NCCN document references fully all its recommendations and is a useful tool for evidence.

The guidelines for the management and treatment of breast cancer can be found on the Greater Manchester & Cheshire Cancer Network Website (www.gmccn.nhs.uk):

Network Breast Imaging Guidelines (11-1C-105b)

Diagnosis

A diagnosis of breast cancer is usually made on the basis of mammography, breast ultrasound and percutaneous biopsy. In some cases MRI is useful.

Staging

In the majority of cases it is only necessary to perform locoregional staging. All women with suspected or diagnosed breast cancer should undergo mammography. It is recommended that ultrasound of the breast be performed in all cases. In general the size of the lesion should be taken to be the greater of the mammographic and ultrasonic measurements.

The standard of care with respect to the axilla is sentinel lymph node biopsy (SLNB) if the axillary lymph nodes appear normal. It is important therefore to perform preoperative ultrasound of the axilla in order to detect overt nodal involvement and prevent unnecessary SLNB and then a further axillary procedure. Nodes with a cortical thickness of >3mm or with eccentric focal cortical thickening or architectural disruption are suspicious of metastatic involvement, and nodes with a cortical thickness of 2.5-3mm are indeterminate. Confirmation of nodal involvement with FNAC or core biopsy is recommended.

Routine staging for metastatic disease at presentation has a low detection rate and has not been demonstrated to confer a survival benefit. However women presenting with locally advanced breast cancer (including inflammatory breast cancer) or clinical evidence of metastatic disease should undergo staging with CT of the neck, thorax, abdomen and pelvis (with IV contrast to demonstrate the liver in the portal venous phase) and isotope bone scanning, as the presence of metastatic disease may influence the choice of treatment and subsequent follow up.

In addition, patients who are found at surgery to have four or more metastatic axillary lymph nodes should be considered for CT staging.

The TNM system has not been in widespread use in the UK for breast cancer staging but is now being used more frequently and its use is encouraged. It is recommended that TNM staging is recorded following primary surgery (this will usually be a combination of pathological T and N stage and clinical M stage). TNM stage should also be reported if preoperative CT staging is performed.

Reporting Of Staging Investigations

Primary tumour

Site: state left or right; quadrant of the breast

Carcinoma in situ	Tis
Tumour >0.1cm but ≤0.5cm	T1a
Tumour >0.5cm but ≤1cm	T1b
Tumour >1cm but ≤2cm	T1c
Tumour >2cm but ≤5cm	T2
Tumour >5cm	T3
Any size with extension to chest wall (excl. pec. major)	T4a
Any size with ulceration, ipsilat. skin nodules, skin oedema	T4b
Both 4a and 4b	T4c
Inflammatory carcinoma	T4d

Nodal status

Regional nodes: axillary (ipsilateral)

Level I – lateral to pectoralis minor

Level II – behind pec. minor inc. the interpectoral nodes

Level III – apical and medial to pec. minor

 infraclavicular (ipsilateral)

 internal mammary (ipsilateral)

 supraclavicular (ipsilateral)

Metastasis in movable ipsilateral level 1 or 2 axillary node(s)	N1
Metastasis in fixed/matted ipsilateral level 1 or 2 axillary node(s)	N2a
Metastasis in ipsilateral internal mammary nodes in absence of axillary node mets	N2b
Metastasis in ipsilateral infraclavicular node(s)	N3a
Metastasis in internal mammary and axillary nodes	N3b
Metastasis in supraclavicular node(s)	N3c

Metastases

State specifically: non-regional nodes, lung, liver, adrenals, kidneys, bone, brain, marrow, pleura, peritoneum, skin other. **M1**

State final TNM stage

Other Investigations

Preoperative MRI of both breasts is indicated in those women in whom the needle core biopsy shows an invasive lobular carcinoma, as these have a higher incidence of multifocality and bilaterality and are more often mammographically occult than other tumour types. Its use should also be considered in young women (esp.

<35years of age) and in those with dense breasts. It should also be performed prior to neoadjuvant chemotherapy if MRI is the intended monitoring modality. MRI is not recommended for routine preoperative use in other groups of women with breast cancer.

Women with locally advanced cancers who are undergoing neoadjuvant chemotherapy or endocrine therapy will need restaging during the treatment to assess response. Mammography, ultrasound or MRI may be used. Marker clip placement within the lesion should be considered prior to commencement of neoadjuvant chemotherapy.

Follow-Up

There is evidence to suggest a survival benefit for women who undergo surveillance mammography after treatment for breast cancer. Hard evidence to support one mammographic follow up regime over another is lacking. The NICE Breast Cancer Quality Standard published in August 2011 should be followed as a minimum:

Women treated for early breast cancer have annual mammography for 5 years after treatment. After 5 years, women who are 50 or older receive breast screening according to the NHS Breast Screening Programme timescales, whereas women younger than 50 continue to have annual mammography until they enter the routine NHS Breast Screening Programme.

Imaging Of Recurrence

Local recurrences in the breast are generally detected on routine follow up mammography or clinical examination and should undergo standard triple assessment.

Ultrasound and FNAC or core biopsy is useful in suspected nodal metastatic disease in the axillae and neck.

CT staging of the neck, thorax, abdomen and pelvis should be considered in patients with locally recurrent breast cancer.

Patients suspected of having distant metastatic disease on the basis of symptoms or signs should be investigated as clinically appropriate with isotope bone scan, plain radiography, CT, ultrasound or MRI.

The following guidelines have been reviewed and agreed by the Breast CSG members on 25 January 2012:

- Royal College of Radiologists, Guidance on Screening and Symptomatic Breast Imaging, April 2005
- Royal College of Radiologists, Breast Imaging Classification, April 2005

Network Breast Pathology Guidelines (11-1C-106b)

The following guidelines have been reviewed and agreed by the Breast CSG members on 25 January 2012:

- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- Royal College of Pathologists, Tissue Pathways for breast pathology, April 2009
- NHS BSP Non-operative diagnosis guidelines (2001)
- HER2 testing in the UK: further update to recommendations. JClin Path July 2008, 61: 818-824
RA Walker, JMS Bartlett, M Dowsett, IO Ellis, AM Hanby, B Jasani, K Miller, SE Pinder
- HER2 testing in the UK: consensus from a national consultation. JClin Path June 2007, 60: 685-689; M Dowsett, AM Hanby, R Laing, R Walker

SECTION 2

Clinical Guidelines for the Management of Breast Cancer in the Greater Manchester & Cheshire Cancer Network

Introduction

- This manual sets out the guidelines on the management of breast cancer to be adopted by the cancer centre and units in the Greater Manchester and Central Cheshire Cancer Network
- All new patients with breast cancer should be discussed by a multi-disciplinary team
- Patients should be considered for clinical trials
- Patients may be treated outside this guidance but this must be agreed by the MDT and the reasons recorded in the patients notes
- Section 4 provides guidance on the management of benign breast disease in this Network

The Structure & Function of the Breast Multi Disciplinary Team (MDT)

The MDT lead should be a single named clinician who is also a core team member

The MDT core team should include: (Peer Review Measure 11-2B-101b)

- Two designated breast surgeons
- Two oncologists, at least one should be Clinical Oncologist. The team should include a Medical Oncologist where the responsibility of chemotherapy is not undertaken by the clinical oncology core team member
- Two imaging specialists
- Two histopathologists
- Two breast nurse specialists
- MDT co-ordinator/administrator
- An NHS employed member of the core or extended team should be nominated as having specific responsibility for users' issues and information for patients and carers
- A member of the core team nominated as the person responsible for ensuring that recruitment into clinical trials and other well-designed studies is integrated into the MDT

The MDT extended team should include: (Peer Review Measure 11-2B-118b)

- A core member of the specialist palliative care team;
- Breast radiographer
- Psychiatrist or clinical psychologist
- Plastic/reconstructive surgeon
- Clinical geneticist / genetics counsellor
- Physiotherapist / lymphoedema practitioner

It is the opinion of the members of the Breast CSG that a Research Nurse also forms part of the extended team, due to the important role in recruiting patients to clinical trials.

Characteristics of an effective MDT:

- Conduct is governed by local policy but should be polite and respectful.
- The MDT may be a forum for teaching and learning.
- The case presentations should be concise and relevant; the question addressed to the MDT should be clearly framed.
- Time thresholds for placing the patient on the MDT should be adhered to except in case of urgency.
- The meeting should allow for full discussion of scheduled cases.
- MDT meetings should be part of all consultant job plans

Imaging In the Diagnosis of Breast Lumps

Age 40yrs and older

- Digital mammography (Two-view mammography if digital not avail)
- +/- Ultrasound

Age <40yrs

- Ultrasound **if imaging is indicated**
- Specific indications for ultrasound
 - Symptomatic or clinically apparent localised area
- Mammography should only be used to assess suspicious lesions identified by USS as an aid to diagnosis

Tissue diagnosis (histology / cytology)

- It is recommended a biopsy should be performed under image guidance
- Aim for a pre-operative diagnosis rate of >90% as per breast screening QA target

The role of other imaging modalities in breast cancer

MRI Scanning – indications for use are:

- Screening of genetic high risk patients (according to family history guidelines or as part of a trial)
- Screening of patients following mantle radiotherapy
- For diagnosis of occult breast primary cancer, suspected on clinical grounds, in patients for whom conventional imaging is unsuccessful, eg malignant axillary nodes
- Lobular breast cancer
- Assessing possible recurrence after previous surgery+ radiotherapy, if mammography is equivocal
- Patients with suspected breast implant problems for greater clarification

PET scanning

No guidelines exist presently

Pre-operative ultrasound of the axilla

- The role of SLNB is to reduce operative morbidity.
- It is preferable to avoid two procedures (SLNB and subsequent clearance).
- Axillary ultrasound followed by core biopsy / FNAC of suspicious LN to demonstrate the presence of malignant involvement at the time of initial diagnostic core.
- Patients with an involved axilla can then proceed directly to axillary node clearance, as per NICE guidance.

Diagnosis

All discrete masses presenting symptomatically must be assessed by imaging (see above) and core biopsy (or fine needle aspiration cytology). **It is now accepted that we should rely primarily on Core Biopsy**

- Core biopsy can be used in conjunction with FNA. Some units may choose to perform core biopsy in all suspected cancers (BASO Guidelines 2009).
- FNA /core biopsy of axillary lymph nodes that are suspicious on ultrasound
- Occasionally Vacora Core Biopsy / mammotome will be required for persistent discord between the various aspects of the triple assessment.
- When a diagnosis is not achieved by less invasive measures – Surgical diagnostic biopsy becomes essential.
- If FNA result is C4 (suspicious), or C3 (atypical), consider target core biopsy to obtain pre-operative diagnosis
- If FNA result is C1 (inadequate/non-diagnostic), when the clinical and imaging findings are malignant, indeterminate or suspicious a core biopsy must be done to obtain a tissue diagnosis

Basic information: The information required on all patients is as follows:-

- Clinical history and examination
- Age and menopausal status
- Past or concurrent medical illnesses
- Family history
- Histologically confirmed diagnosis of breast cancer (core biopsy as minimum)
- Drug history & allergies

Data Collection

SCR (Somerset Cancer Registry) Database

- This will be up-loaded to form part of regional and national data.
- It also enables treatment planning and electronic record keeping.
- The SCR should be uploaded live at the time of the MDT

Patients listed for Primary Breast Cancer surgery should have:

- Full blood count
- Biochemical profile (bone and liver function tests)

Pathology Reporting

Pathology Reporting will follow the guidelines given in "Pathology Reporting of Breast Disease" NHSBSP, publication no 58 issued January 2005 by RCPATH and NHSBSP.

<http://www.rcpath.org/resources/pdf/PathologyReportingOfBreastDisease-CORRECTED-lowres.pdf>

This covers scoring for ER and sentinel node reporting. The advice given in the recent national breast pathology update course was that centres already doing PR should continue to do so as it is a proven prognostic indicator. This is contrary to current NICE guidance.

- Tumour size, Histological grade, ER/PR status, AND HER 2 status should be available at the MDT meeting to support:
 - Clinical decision making & treatment planning
 - Recruitment to clinical trials
 - Consideration of neo-adjuvant treatment
- ER, PR and HER 2 will continue to be tested at present. This gives specific information as to the identity of 'Triple negative tumours' which are a separate sub group and may be treated differently.
- The ER and PR will continue to be expressed as a percentage and as Allred score
- HER-2 status can assist in treatment decisions and may become a factor in relapse risk assessment, including the use of Trastuzumab in the treatment of metastatic disease. It is recommended in all patients.
- Receptor requests can be processed on the core biopsy or operative specimen
- An individual should be named within each pathology laboratory to ensure that cores are routinely sent for analysis. This person will also arrange to resend future specimens should results be equivocal.
- Nodal status; sentinel lymph node biopsy should form the standard of care for all patients (within NICE guidelines). A positive sample for macro or micro metastases should always be followed by the consideration for axillary clearance.
- Isolated tumor cells would indicate no further treatment to the axilla is required.
- At the time of the treatment MDT the patient's grade, histological subtype, and **TNM** should be agreed and entered onto the SCR system. (Clinical M stage is satisfactory, even if subsequent data may result in future modification). ER, PR and HER2 should be available for discussion at the MDT meeting.

Staging

Current intelligence and data on cancer stage at diagnosis is not yet robust enough to be used for reliable outcomes analysis. Good quality staging data will continue to be required by local commissioners / consortia to monitor effectiveness of local prevention programmes as we move into more outcome-driven commissioning arrangements.

Less later-stage referrals have clear patient experience and outcomes benefits, but could also potentially mean less intensive use of Trust resources and therefore cost savings for the NHS generally.

As well as forming part of the Acute Trust Contract, collection of staging data is specifically requested in the Operating Framework for the NHS in England 2011/12 and is a focus of the 2011/12 National Peer Review Clinical Lines of Enquiry for a number of other tumours. It may appear as a CLE for Breast Cancer services in future rounds of Peer Review.

To enable Trusts, the Cancer Network and Commissioners to deliver improvements around the collection of staging data, NHS North West have agreed a target of recording stage for 70% of patients discussed at MDT. This target is in line with the one used by the best performing region in the country and is also being discussed as a future cancer target nationally.

The recorded stage should be TNM system.

High risk patients

- High risk is **defined** as definitely greater than 4 lymph nodes involved after a clearance,
- Any patient deemed by the MDT to be high risk should be fully staged.
- Staging investigations include
 - CT scan of thorax abdomen and pelvis (should be performed in the local cancer unit planning to treat the patient)
 - Bone scan
 - Plain films of areas of metastatic disease to compliment bone scans +/- MRI (e.g. hips/femorii).

Risk Stratification

- Endocrine responsiveness has been removed as a risk factor from the St Gallen Consensus, 2005, (Goldhirsch A. et al. Annals of Oncology 16:1569-1583). This is because it is the primary factor in determining treatment.
- Nodal positivity is the most important. However, the presence of micro-metastasis or isolated Tumour cells in lymph nodes should not influence risk allocation and treatment choice
- Her 2 positivity (over expression predicts for responsiveness to anthracyclines and taxanes and lower probability of response to tamoxifen)
- Tumour size
- Tumour grade (not Ki 67)
- Peritumoural vessel invasion, especially lymphovascular invasion

NB: Endocrine responsiveness means strongly ER/PR +ve, (>3/8) and non-responsive refers to ER and PR -ve (<3/8). Absence of PR indicates malfunction of ER signalling and is associated with tamoxifen resistance and possibly ERGR and Her 2 positivity.

FISH testing should be used for patients who are HER-2 positive

Primary endocrine therapy is a treatment option in the case of medical contra-indications or patient preference.

Chemotherapy and tamoxifen should be administered sequentially.

Prognostification and prediction

- The use of microarray (Oncotype DX or Dutch 70 gene array) is increasing worldwide. They are used infrequently in the UK and are not generally funded. It is available in the context of a trial at Christie Hospital
- Such techniques will be useful to determine patients for whom chemotherapy may be avoided, or even to specify the choice of chemotherapeutic agent.
- Adjuvant online (www.adjuvantonline.com) is a free web based program that predicts, based on published data, the statistical impact of therapeutic interventions on a patient. This should be used, in conjunction with clinical expertise, to formulate a treatment plan for a patient.
- Other programmes are available, eg Cambridge, Wishart, & Memorial Sloane Kettering nomogram for prediction of sentinel lymph node positivity

MANAGEMENT OF DUCTAL CARCINOMA IN SITU (DCIS)

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 3.7, p10 - 11)

Introduction

- Surgery must aim to produce complete excision. DCIS is the earliest form of malignancy that is recognised within the breast, and the patients may regard it as pre-cancerous. If a biopsy is reported as incompletely excised (<1mm circumferential margin), then further wide excision must be offered.
- Completeness of excision will depend to some extent on whether the DCIS is unicentric or multicentric. If it is unicentric (<4cm), then the woman may well be suitable for breast conserving surgery, depending on the size of the breast in relation to the size of the DCIS. Patients with multicentric disease have widespread field changes in the breast and should be offered a total mastectomy (see below for axillary surgery in these patients). Complete excision with clear margins (>1mm and clear cavity shavings) is associated with a low recurrence rate. Radiotherapy is not a substitute for adequate surgical clearance.
- Re-excision is required if only one margin is involved but if several margins are involved, mastectomy should be considered.
- If conservation surgery is successful, it is essential the patient has yearly mammograms for at least the first 5 years to provide early detection of any recurrence.
- Patients who are undergoing mastectomy for DCIS should be offered the option of reconstruction and this may be carried out at the same time as mastectomy.

Sentinel Node Biopsy for DCIS

By definition all axillary nodes should be negative in patients with DCIS and therefore sentinel node biopsy is not necessary. However, in certain circumstances sentinel node biopsy should be considered. These are presented below and such patients should be discussed at MDT level.

1. DCIS > 5cm - 50% of these patients will harbour invasive disease within the area of DCIS
2. DCIS presenting as a mass lesion – either a clinical mass or a radiological mass lesion
3. DCIS of high grade in premenopausal patients
4. When doing Mastectomy for DCIS

Adjuvant Radiotherapy for DCIS

- Whole breast radiotherapy reduces the risk of ipsilateral breast relapse after complete excision of DCIS. Randomised trials indicate adjuvant radiotherapy approximately halves the risk of recurrent DCIS and invasive disease [Fisher B, 1998, Julien JP, 2000, UKCCCR DCIS Working party, 2003].
- Radiotherapy should be offered to patients at an increased risk of recurrence and this essentially constitutes all women with high-grade DCIS tumours. Other risk factors for recurrence include tumour size, close margins and presence of comedo necrosis [Silverstein 2003].
- In practice radiotherapy is often omitted in patients considered at low risk of recurrence.
- The long term safety of omitting radiotherapy in low-risk patients is currently being evaluated in randomised trials in the UK and USA.
- No adjuvant radiotherapy is required for women who have undergone mastectomy for DCIS.

LOBULAR CARCINOMA IN SITU (LCIS)

- Marker of increased risk of invasive breast cancer
- Usually an incidental finding
- Close monitoring advised (annual screening)
- There is no indication for adjuvant hormone therapy outside clinical trials
- Pleiomorphic LCIS may need open diagnostic biopsy

THE SURGICAL MANAGEMENT OF INVASIVE BREAST CANCER

- The patient's treatment should have been discussed in the diagnostic MDT.
- All appropriate surgical treatment options, including sentinel lymph node biopsy, axillary node clearance, axillary node sampling, wide local excision, therapeutic mammoplasty, mastectomy, immediate or delayed reconstruction should be discussed and made available and documented in patient case notes.
- If an appropriate option is not locally available the patient should be offered this option and referred appropriately
- Surgical technique is to be of the standard set out by the Royal College of Surgeons.

Indications for surgical treatment

Breast conservation

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 3.2, p7 - 8)

- Numerous randomised clinical trials have demonstrated no differences in overall survival or distant metastases in women with operable breast cancer treated with mastectomy compared to those treated with breast-conserving surgery followed by adjuvant radiotherapy [Fisher 1989, Veronesi 1990, Jacobson 1995, Blichert-Toft 1990]
- The aim of breast conserving surgery is removal of the primary tumour with clear histological margins. It is recommended that the margins of excision are examined by the pathologist following "inking" of the specimen and that the specimen is orientated to ensure that the appropriate margin can be identified (if one is involved). If the lesion is screen detected and impalpable (and therefore surgical excision is radiologically guided) it is mandatory to perform a specimen X-ray intraoperatively (NHS Breast Screening Programme recommendation). Due to the recognised difficulty of assessing excision margins, it is helpful to perform cavity biopsy shavings to assess excision status. Where clear excision margins cannot be achieved, re-excision or mastectomy is advised.
- The size of the tumour that can be excised with adequate cosmesis depends on the size of the breast. For example a 2cm tumour in a small breast may not be suitable for breast conservation. Conversely, a 4cm tumour in a lady with large breasts may be suitable for a therapeutic mammoplasty utilizing for example "reduction-type" incisions. Patients opting for this type of surgery should be warned that if the tumour margins are involved then a completion mastectomy would be required unless the surgeon can be confident of exactly where the involved margin is sitting within the remodelled breast. Contralateral reduction surgery can be carried out at the same time but again the patient should be warned about asymmetry following radiotherapy to the affected breast. If the patient has a large tumour but requires conservation she may be offered preoperative systemic therapy (see section 5).
- The use of titanium **surgical clips** to localise the tumour bed is recommended to facilitate the planning tumour bed boost and partial breast radiotherapy. Clips should be positioned in pairs at the medial, lateral, superior, inferior and deep cavity edges at the time of surgery.

Special Points of Surgical Patient Management

- Wide local excision, network guidelines $\geq 1.5\text{mm}$ margins
- Clips to mark the cavity in all patients (to aid radiotherapy planning)
- Orientation of specimen is important for margins assessment
- Clearance of margins must be documented and discussed at MDT

Mastectomy

Patient selection

- Multi focal or multicentric disease affecting more than one quadrant
- Tumour central and behind nipple (can consider central or grissotti excision oncoplastic techniques)
- Size of breast would give unacceptable cosmetic result with conservation surgery
- Recurrence after breast conservation and RT
- Patient refuses breast radiotherapy or is contraindicated
- Patient choice
- Incomplete wide local excision despite 2 attempts at breast conserving surgery
- Extensive in-situ component
- Relative contraindications to adjuvant radiotherapy, ie.
 - 1st or 2nd trimester pregnancy
 - Active scleroderma
 - Active systemic lupus erythematosus

Surgical management of axilla

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 3.8, p11 - 12)

- The intention of axillary surgery is to provide control of disease within the axilla and to provide prognostic information for the patient which may be of importance in planning subsequent treatment. Axillary lymph node status remains the most powerful prognostic indicator for early breast cancer.
- Axillary surgery is indicated for all patients with invasive breast cancer, but is not routinely indicated for patients with pure DCIS (see above).
- There are two principle surgical approaches:
 - **Sentinel node biopsy** in which the sentinel node is identified and excised. It is not appropriate if palpable axillary nodes are present. Patients with negative nodes require no further axillary treatment while those with positive nodes (macrometastases or micrometastases, but **not** isolated tumour cells) go on to have a surgical clearance of the axilla, or, where this is not possible, then nodal radiotherapy. The comparison of these latter two options is being undertaken in the AMAROS trial.
 - **Level III axillary clearance** in which all lymph nodes up to the apex of the axilla are removed.

Sentinel node biopsy

- This technique should be considered for patients in whom there is no palpable axillary lymphadenopathy.
- The axilla should be assessed using a “triple assessment” approach i.e. clinical examination followed by ultrasound scan and FNA/core biopsy of nodes with an abnormal appearance on ultrasonic assessment. Following such an assessment those patients with cytologically proven axillary node metastases should proceed directly to level 3 axillary node clearance. Those patients with no palpable axillary nodes and normal ultrasound appearances of the axillary node architecture can proceed to sentinel lymph node biopsy.
- The issue with the sentinel node technique is the risk of a false negative and then subsequent axillary recurrence. Surgeons performing sentinel node biopsy need, therefore, to be able to demonstrate a false negative rate of 5% or less. To improve accuracy, both radioisotope and blue dye localisation should be performed. If blue dye is used patients need to know the very rare but potentially serious side effect of anaphylaxis. If the sentinel node biopsy is positive, either axillary radiotherapy or axillary clearance will be necessary.

Axillary Clearance

The extent of axillary dissection is defined with reference to the pectoralis minor muscle:

- Level I - lower axilla up to the lower lateral border of the pectoralis minor.
- Level II - axillary contents up to the medial border of the pectoralis minor.
- Level III - axillary contents extending to the apex of the axilla.

Level III axillary clearance is absolutely indicated for the following patients

- cytologically proven axillary lymph node metastases

Level III axillary clearance is relatively indicated for the following patients and should be discussed at MDT level on a case by case basis

- patients with previous axillary surgery and current ipsilateral breast cancer diagnosis
- patients with inflammatory breast cancer
- patients receiving neoadjuvant chemotherapy for very large / advanced breast cancer
- patients wishing to completely eliminate the possible need for a second axillary operation if a sentinel node procedure yields a positive node (could have axillary irradiation).

Reconstruction after mastectomy

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 3.8, p11 - 12)

- Reconstruction is oncologically safe
- All patients should be offered reconstruction – immediate or delayed.
- If immediate reconstruction is being considered, consider SLNB first in LD & abdo flaps. This is not necessary for tissue expanders.
- Immediate reconstruction may not be suitable for the following groups as many of these patients may also require post-operative radiotherapy.
 - Patients with primary tumours >4cm
 - Node positive tumours (esp if grade 3)
 - Locally advanced disease
 - Inflammatory cancers (absolute contraindication)
 - Large cancers down-staged by neo-adjuvant chemotherapy
 - Where there is clear pre-operative evidence of extensive lymphatic/lymphovascular space invasion
 - In the presence of severe co-morbidity
- Smokers and medically unfit may not be suitable for reconstruction
- It must be recognised that breast reconstruction is not a single operation to completion. Further minor operations will be required which can include nipple and areola complex reconstruction and symmetrisation procedures.
- Patients considering breast reconstruction should have the techniques, limitations, complications, and outcomes fully discussed, as well as expectations and aesthetic ambitions. Additionally the specialist breast care nurse will spend time talking to the patient and they will be shown photographs of different outcomes to help them make their choices. The risk of potentially delaying adjuvant treatment should be explored to ensure an oncoplastic balance is achieved and that the patient is informed prior to consent. All patients undergoing breast reconstruction must have pre-operative and post-operative photographs both for the medical records and for medico-legal reasons.
- For women where there are local issues in providing breast reconstruction there should be arrangements made by that trust to refer to the most appropriate unit in a timely manner especially when immediate reconstruction is required. For those women who are keen on using abdominal wall tissue for reconstruction they can be referred as per the GMCCN immediate breast reconstruction pattern (see below) for consideration of a free flap e.g. DIEP (deep inferior epigastric perforator)

- Any reconstruction option selected by a patient and not available locally needs to be referred as per the network protocol

GMCCN Immediate Reconstruction Referral Patterns

Breast MDT	Named specialist breast reconstruction surgeon	Named cover	Named specialist for free flap surgery
Bolton	Jane Ooi Tibor Kovacs	Tibor Kovacs Jane Ooi	Victoria Rose Ken Graham
East Cheshire	Chandeena Roshanlall Jalal Koken	Jalal Koken Chandeena Roshanlall	Gary Ross Stuart Wilson
Mid Cheshire	Vanessa Pope Gopal Mahadev	Gopal Mahadev Vanessa Pope	Stuart Wilson / Victoria Rose
Pennine	Janet Walls / Shamin Absar / Maria Bramley	Janet Walls / Shamin Absar / Maria Bramley	Victoria Rose Ken Graham
Salford	Zahida Saad Sumohan Chatterjee	Sumohan Chatterjee Zahida Saad	Stuart Wilson / Victoria Rose
Stockport	Mr Amir Sharif	No cover	Stuart Wilson / Victoria Rose
Tameside	Mr Pardeep Arora	No cover	Stuart Wilson / Victoria Rose
UHSM	Andrew Baildam / Lester Barr / Ged Byrne / Nigel Bundred / Richard Johnson / Ashu Gandhi / Asaid Zeiton	Andrew Baildam / Lester Barr / Ged Byrne / Nigel Bundred / Richard Johnson / Ashu Gandhi / Asaid Zeiton	Victoria Rose / Stuart Wilson Gary Ross
Wigan	Richard Harland / Amar Deshpande / Ram Prasad	Richard Harland / Amar Deshpande / Ram Prasad	Ken Graham

Medically unfit patients

- Surgery is best for control of local disease (either wide-local excision or mastectomy)
- Anaesthetic opinion may be necessary
- Biopsy is required to confirm diagnosis and establish endocrine responsiveness
- Primary endocrine therapy using letrozole if endocrine responsive (Eierman W. et al Annals of Oncol vol 12 no. 11 (2001) pp 1527-1532).
- Management of the axilla is individually determined according to the performance status, stage and patients' wishes
- If inoperable for consideration of Radiotherapy, Systemic therapy, and Palliative Care should be given

ADJUVANT RADIOTHERAPY

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 5, p16 - 21)

Adjuvant radiotherapy reduces both local recurrence and breast cancer mortality. For every 4 local recurrences that are prevented, one breast cancer death is avoided [EBCTCG 2005].

Radiotherapy following breast conserving surgery

- In selected patients, this gives equivalent survival and control of local disease to mastectomy [Fisher 1989, Veronesi 1990, Jacobson 1995, Blichert-Toft 1992].
- A systematic overview by the Early Breast Cancer Collaborative Group has shown that adjuvant radiotherapy reduces 5 year local recurrence rates from 26% to 7% and reduces 15 year breast cancer mortality from 35.9% to 30.5%. [EBCTCG 2005]. The relative benefits are similar after mastectomy or breast conserving surgery, in the presence or absence of adjuvant systemic therapies and in both axillary node-negative and positive patients. The absolute benefits depend on prognosis. The use of adjuvant radiotherapy corresponds to 1-5 additional node-negative women and 5-10 additional node-positive women being alive at 10 years for every 100 women treated.
- In a series of 2299 patients treated at the Christie between 1989 and 1992, the breast local relapse rate was 6.3 % at 5 years [McBain CA 2003]. Approximately 50% of these recurrent patients were salvaged by subsequent surgery, usually a mastectomy. For NHSBSP screen detected cancers the breast recurrence rate was only 4 %.
- A decade later (1999-2001) the START trial reported a 3% loco-regional recurrence rate at 6 years [The START Trialists' Group 2008]. Careful follow up is needed to detect salvageable recurrence.
- The patient must wish to preserve her breast; she must be medically fit enough, and willing to undertake a course of radiotherapy.

Selective avoidance of radiotherapy following breast conserving surgery

A group of patients can be identified where the risk of local recurrence without XRT is low. However clinical trials to date have shown that even in patients who are considered to have a low risk of local recurrence, the use of adjuvant radiotherapy will reduce their risk even further [Fisher 2002, Fyles 2004]. One trial in patients over 70, T1 N0 ER positive, has reported a 9% relapse rate with surgery and Tamoxifen versus 2% with surgery, tamoxifen and radiotherapy [Hughes 2010]. Survival was identical. Giving XRT in this low risk group will only benefit a minority of patients but clearly gives inconvenience, discomfort and a small risk of serious morbidity to the majority. Omitting XRT will not prejudice the patient's chance of survival. Careful follow-up will allow most recurrences to be detected early and further breast-conserving surgery to be used at the time of relapse.

Avoiding radiotherapy after breast conserving surgery is an option which can be considered in certain selected patients, who meet the following criteria.

- Screen – detected
- Post menopausal
- Endocrine-responsive
- Path node negative
- Tumour size < 1cm
- Clear margins
- Patient consent
- Ability to attend for annual mammography

Only a minority of patients (< 10%) will meet these criteria. The remainder will still require radiotherapy after surgery to minimise the risk of local recurrence.

Radiotherapy should not be avoided in the following situations

- grade 3
- lobular cancers
- extensive DCIS

Radiotherapy following mastectomy

A systematic overview has shown that post-mastectomy radiotherapy reduces 5 year local recurrence rates from 23% to 6% and breast cancer mortality from 60.1% to 54.7%. There was an absolute overall mortality reduction of 4.4% [EBCTCG 2005].

A meta-analysis of post-mastectomy radiotherapy trials using **modern** radiotherapy techniques confirm an overall survival gain with no excess non-breast cancer mortality [Whelan 2000].

Radiotherapy to the chest wall is only indicated after mastectomy in certain situations where there is a high risk of local recurrence and where radiotherapy has been demonstrated to reduce the risk of local recurrence.

Recommendations based on NCCN Clinical Practice Guidelines 2009.

- Large primary tumours > 5 cm (**absolute** indication). Consider also for smaller tumours in very small breasts.
- Tumours incompletely excised e.g. tumour at the deep resection margin, or invading muscle or skin (**absolute** indications).
N2 and N3 disease (**absolute** indication).
- Occasionally chest wall irradiation is given to patients who do not fulfil the above criteria but where the primary tumour shows particularly aggressive histological features (e.g. extensive lymphovascular invasion in a Grade 3 tumour, or a grade 3 tumour with close posterior margins). There is no evidence that adjuvant radiotherapy reduces the risk of local recurrence in such cases. However, where the overall likelihood of recurrence is considered high, due to a combination of risk factors, then radiotherapy to the chest wall may be considered (**relative indication**).

Radiotherapy to Internal Mammary Nodes

- Sentinel lymph nodes studies indicate that only a very small proportion of patients have sentinel nodes in the IMN chain.
- Clinical recurrence in the IMN chain is relatively rare, even without IMN radiation.
- The potential benefits of IMN radiotherapy are currently being addressed in the EORTC trial 22922 and the Canadian MA.20 trial.
- Long term toxicity data (eg cardiovascular) are required in the setting of modern radiotherapy techniques and adjuvant systemic therapies.
- Routine prophylactic irradiation of the internal mammary nodes is not advised.
- If internal mammary nodes are **known** to be positive (e.g. after sentinel node biopsy) then an individualised CT planned treatment to include the internal mammary chain needs to be discussed with the radiotherapy planning department.

Radiotherapy techniques

Whole breast radiotherapy after breast conserving surgery.

- Skin bolus is not used routinely.
- A mid-plane dose of 40 Gy in 15 fractions over 3 weeks is used.
- Occasionally shorter course regimens may be used, particularly in patients with poor performance status and significant co-morbidities. 30 Gy in 8 daily fractions or 30Gy in 5 weekly fractions.

Tumour bed boost

Boost radiotherapy to the tumour bed has been demonstrated to reduce local recurrence rates following breast-conserving surgery. The greatest benefit is seen in patients under 40 years of age and a moderate benefit is seen in women between 40 and 50 years of age. Less benefit is seen in women over 50 years of age [Bartelink 2001].

In view of these findings we recommend that boosts are given **at least** to the following groups:

- Women under 40 years of age
- Women between 40 and 50 years of age who are at high risk of local recurrence (grade III, extensive lymphovascular invasion)
- Women of any age with involved surgical margins (< 1 mm)

It is preferable that the boost is planned using information from the pathology report, surgical notes and pre-op mammograms. Surgical clips in the tumour bed, if present, also aid localisation.

Partial breast radiotherapy

- The use of partial breast radiotherapy delivered using intensity modulated techniques following complete tumour excision in women with low risk early stage breast cancer has recently been evaluated in the IMPORT LOW trial, and the results are awaited.
- A randomised trial of intra-operative radiotherapy has shown local recurrence rates of 1.2% at 4 yrs compared to 0.95% for external beam whole breast radiotherapy [Vaidya 2010].
- Pending the results of randomised trials using external beam treatments, partial breast radiotherapy could be considered for patients who
 - Fit the criteria outlined by the ASTRO consensus (≥ 60 years, T1, N0, ER +ve, Margins ≥ 2 mm, IDC, or other favourable histological subtypes, no LVI, no BRCA 1/2, unifocal) [Smith 2009].

AND

- Where the tumour bed is easily identifiable with surgical clips or a seroma visible on ultrasound or CT scan.

Regional nodal radiotherapy.

- A supraclavicular fossa field, with lateral margins just medial to the glenoid cavity, and medial margins at the midline, may be used if axillary irradiation is not required, particularly after a full level 3 clearance, as this is associated with a lower incidence of lymphoedema. Indications would include involvement of 4 or more axillary nodes after a level 3 clearance
- Irradiation of a target volume including the full axilla and supraclavicular fossa en bloc is indicated:
 - a) After positive axillary sampling procedure, and
 - b) Where there is inoperable axillary disease (eg>10 positive nodes and / or extensive extracapsular spread)

Then radiotherapy to the supraclavicular fossa and axilla may be considered, if the risks of axillary recurrence are thought to outweigh the considerable risks of treatment toxicity, in particular lymphoedema.

Integrating chemotherapy/radiotherapy

- There are few prospective data available on the optimum sequence of chemotherapy and radiotherapy. Simultaneous chemotherapy and radiotherapy is avoided. The preferred option is to give radiotherapy after chemotherapy is completed (essential if anthracyclines are used).

Radiotherapy for patients treated by mastectomy and immediate reconstruction

- Patients treated by means of mastectomy and immediate reconstruction should normally have small tumours with good prognosis and, therefore, radiotherapy will not be required.

- In patients where pre-operative assessment reveals clinical features indicating the possible need for post-operative radiotherapy, immediate reconstruction may not be appropriate.
- However, there will be situations where mastectomy and immediate reconstruction is carried out and the patient is found to have higher risk disease where post mastectomy radiotherapy would normally be advised. When required on clinical grounds, there is no absolute contraindication to radiotherapy in a patient with a breast prosthesis in situ or with a myo-cutaneous flap. However, the tissues around the prosthesis may, on occasion, shrink following radiotherapy and cause pain, requiring removal of the prosthesis. The patient should be advised that radiotherapy may impair the cosmetic and functional result.

PREOPERATIVE (NEO-ADJUVANT) THERAPY

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 6, p23 - 21)

Aims of treatment

- To reduce the size of large tumours in order to perform breast conserving therapy
- To eliminate systemic micro-metastases if present (as in postoperative therapy)
- To obtain prognostic information (tumour response)
- To obtain biological (predictive) information for research purposes

Rationale

- **Locally advanced.** Neo-adjuvant therapy is currently the standard of care in locally advanced breast cancer to facilitate potentially curative surgery. Partial or complete tumour responses occur in the majority (~80%) of such tumours during combination chemotherapy. However, significant differences in histo-pathological response rates are observed for tumours of different pathological phenotypes.
- **T2 and T3 tumours.** Neo-adjuvant chemotherapy increases breast conservation rates but no survival advantage has consistently been demonstrated over post-operative chemotherapy [Fisher 1998, Van der Hage 2001, Scholl 1994].

Patient selection

- Patients with large tumours that would normally require mastectomy but who wish to have breast conservation.
- Tumours would normally be greater than 3 cm in size. However patients with smaller tumours in small breasts may also require pre-operative chemotherapy for conservation.
- Neo-adjuvant cytotoxic therapy is generally not advisable for grade 1 ER and PgR expressing breast cancer.

Chemotherapy

- The best pre-operative chemotherapy regimen has not been identified. However pathological complete response (pCR) has been identified as an excellent prognostic factor [Fisher 1998] and new regimens are tested in neo-adjuvant trials with pCR as the primary endpoint. These indicate that regimens containing anthracyclines +/- taxanes have highest pCR rates.
- The NSABP B-27 trial demonstrated the superiority of 4AC followed by 4 Taxotere pre-operatively compared to 4AC alone pre-operatively and 4AC preoperatively with 4Taxotere given post-operatively in terms of improved pCR rates, although no difference in DFS or OS was found [Bear 2006].

Suggested regimens for neo-adjuvant chemotherapy

- FEC (E75-100mg/m²) x 6-8 cycles
- FEC x 3-4 followed by Docetaxel 100mg/m² x 3-4

Trastuzumab (Herceptin)

- The addition of concurrent trastuzumab to neo-adjuvant taxane containing chemotherapy in women with HER2 over-expressing tumours increases the pCR rate, but has no significant impact on survival [Budzar 2005]. Cardiac toxicity may become an issue with combination epirubicin and trastuzumab and, as such, remains a regimen for clinical trials. Combination of trastuzumab with docetaxel (either FEC – TH or TCH regimens) should be considered for HER-2 over-expressing tumours.

Endocrine Therapy

- Hormone receptor positive tumours respond relatively less well to neo-adjuvant chemotherapy than receptor negative tumours [Von Minckwitz 2005, Untch 2002, Kuerer 199, Colleoni 2001].
- Primary endocrine therapy with anastrozole has been shown to be as effective as four cycles of AT in patients with ER positive breast cancer [Semiglazov 2007].
- Postmenopausal women with locally advanced tumours expressing high levels of ER and PgR could be considered for neo-adjuvant endocrine therapy, particularly in the presence of co-morbid conditions and poor performance status.
- AIs have demonstrated superiority over tamoxifen in terms of response rates and facilitation of breast conserving surgery in post menopausal women [Smith 2005, Ellis 2001].
- The optimum duration of neo-adjuvant endocrine therapy is not known. In the absence of progression treatment should continue for 4 months. If no objective response is seen at this point treatment should be discontinued. If response is seen then treatment should continue for up to 12 months or when BCS becomes feasible or the first suggestion of disease progression – whichever comes sooner.

Procedure

A core biopsy must confirm invasive carcinoma

- A full explanation of the procedure should be given to the patients including information that breast conservation may not necessarily be possible even after chemotherapy.
- Tumour size should be estimated by clinical measurement, mammography and ultrasound before treatment begins (baseline). Clinical measurements should be repeated each visit and mammography and ultrasound half way through and at the end of treatment (pre surgery).
- If the response to treatment is good and breast conserving surgery is anticipated the patient should be referred back to her surgeon for consideration of placement of a clip in the tumour to aid in the surgical excision of the tumour bed and in histological assessment.
- Treatment should continue as long as there is no increase in tumour size. Clinical stability can represent pathological response and late responses occur with a switch in class of chemotherapy.
- Conservation surgery should be by quadrantectomy or wide excision. It is important to take shavings of the tumour bed. If a small area of micro-calcification was present in the original tumour complete excision of the area must be confirmed by specimen x-ray. Surgery is advised 3-4 weeks after the final chemotherapy injection and when blood counts have recovered.
- Complete axillary dissection is advised to prevent recurrence, reduce the need for axillary radiation, and to give prognostic information. There is limited data on the role of sentinel node biopsy after primary medical therapy and this is not recommended.
- Post mastectomy radiotherapy should be based on the initial tumour and lymph node characteristics. Even after cPR and mastectomy the local recurrence rates are high if the original tumour was large or heavy lymph node involvement was present.

ADJUVANT CHEMOTHERAPY

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 7, p26 - 37)

Aims of Management

- To select patients who require adjuvant therapy
- To select appropriate adjuvant therapies
- To enter patients into clinical trials since the benefits of current therapy are modest.

Assessment of Risk

There are a number of major risk factors for the development of metastases. Nodal status remains the most important prognostic factor, followed by tumour size. However factors other than stage alone are also predictive of poor prognosis. Such factors include histological grade, with grade III tumours having a worse prognosis than grade I tumours; young age (<35 years) HER2 over-expression, lymphovascular invasion and high proliferation rates (Ki-67). Estrogen and Progesterone receptor (ER) expression are associated with a better prognosis and ER expression is predictive of a response to endocrine therapy [EBCTCG 2005].

A number of tools are available to clinicians to allow an estimation of a patient's prognosis from the above prognostic factors:

The Nottingham Prognostic Index (NPI) [Haybrittle 1982].

The NPI estimates prognosis in early breast cancer following surgery and radiotherapy but without systemic therapy:

NPI= tumour grade (1-3) + lymph node stage (1-3) + 0.2 x tumour size in centimetres.

An NPI of < 2.4 is associated with an excellent prognosis, similar to that of the normal population; 2.4-3.4 gives a good prognosis with an 80% 10 year survival; 3.4-5.4 gives an intermediate prognosis and a 50-60% 10 year survival and an NPI of > 5.4 is associated with a poor prognosis and a 10 year survival of less than 20%.

The NPI does not take into account many other prognostic factors including Her2 and ER/PR.

St Gallen Risk Categories [Goldhirsch 2007]

LOW	INTERMEDIATE	HIGH
<p>≤ 2 cm <i>and</i> Grade 1 <i>and</i> Node –ve <i>and</i> ER and/or PR positive</p> <p><i>and</i></p> <p>Her2/neu not over-expressed or amplified <i>and</i> Age ≥ 35 <i>and</i> Absence of extensive peri-tumoural vascular invasion</p>	<p>Node –ve <i>and at least one of:</i></p> <ul style="list-style-type: none"> • > 2cm • Grade 2-3 • Extensive peri-tumoural vascular invasion • ER and PR negative • Her2/neu over-expressed or amplified • Age < 35 <p>1-3 Nodes <i>and</i></p> <ul style="list-style-type: none"> • ER/PR positive <i>and</i> • Her2/neu not over-expressed or amplified 	<p>1-3 Nodes <i>and</i></p> <ul style="list-style-type: none"> • Her2/neu over-expressed or amplified <i>or</i> • ER/PR negative <p>4+ Nodes</p>

Adjuvant! Online (www.adjuvantonline.com) [Ravdin 1996]

Adjuvant! Online gives estimates of 10 year breast cancer specific and overall survival rates for untreated patients based on rates observed in the SEER registry for women diagnosed between 1988 and 1992 and gives estimates of adjuvant treatment efficacy based on data from the EBCTCG meta-analyses as well as single trial data and unlike the NPI allows ER status and the patients age and co-morbidities to be factored in. Adjuvant! does not, however, take into account the implications of HER2 over-expression nor the presence or absence of lympho-vascular invasion though the user can add an allowance for increased risk. The accuracy of the tool is less for the very young and the elderly patient with breast cancer. Recent data suggests that Adjuvant! Online may over-estimate overall survival in the UK by about 5% and may therefore underestimate gains from adjuvant systemic therapy (Campbell, Taylor et al. 2009).

Adjuvant!Online allows the clinician to have an estimation of the absolute benefits of adjuvant treatment for any given patient. The absolute benefits for any patient are therefore dependent on that patient's risk of recurrence ie their prognosis. For example if a treatment is associated with a 25% reduction in the relative risk of death at 10 years (a hazard function of 0.75) then a patient whose risk of recurrence at 10 years is 10% will have an absolute benefit of 2.5% from that treatment (ie if 100 patients are given that treatment 2-3 lives will be saved). If the patient's risk of recurrence at 10 years is 40% then the absolute benefit of that same treatment is 10%. Tools such as Adjuvant! can be useful as decision aids to allow patients to have a more informed decision about the potential benefits or otherwise of chemotherapy and allow them a better understanding of the risk: benefit ratio.

'Predict' is an alternative predictive programme (www.predict.nhs.uk)

Proliferation markers and multi-gene signatures

One area of rapid progress is in the distinction between endocrine sensitive but chemotherapy resistant tumours of luminal A subtype from those of luminal B, which are relatively endocrine resistant and chemo-sensitive. Ki-67 may be a useful factor in differentiating between the luminal subtypes although cut off values to define high vs low subgroups vary significantly between published studies (3.5-34%) [Yerushalmi 2010]. Use of the median Ki67 value to define this cut point has been adopted in the majority of such studies although significant heterogeneity in the median values exists (3.5-28%) [de Azambuja 2007]. In Manchester the median Ki67 value for grade II breast tumours assessed at the Christie Hospital 2006-2010 with strong ER and PR expression (QS 7-8) was 18%.

Furthermore proliferation is the most important part of multi-gene signatures and has led to a better understanding of the biology of Elston grade 2 tumours. Grade 2 cancers can be dichotomised into low grade (two thirds of cases) and high grade (one third) tumours by assessing their proliferative or 'genomic grade' signatures [Ivshina 2006, Loi 2007, Wirapati 2008]. Screen detected cancers demonstrate reduced proliferative rates compared to stage matched symptomatic tumours and should be treated according to measured biological factors rather than by method of detection alone. This is an evolving field of research. Although an un-validated approach at the time of writing, it may in future be possible to input quantitative ER/PR, Ki67 and Her2 into a novel algorithm termed IHC4 which has demonstrated similar capacity to predict relapse free survival as the well validated Oncotype DX assay.

Referral for Adjuvant Chemotherapy

Clinical trials and the Oxford Overview analysis have clearly demonstrated the benefit of adjuvant chemotherapy using a combination of drugs over a prolonged course (4-6 months) [EBCTCG 2005]. The benefits of chemotherapy are greatest in young women under 50 and in women with ER negative or Her-2 positive breast cancer. For example anthracycline-based chemotherapy reduces the annual death rate from breast cancer by 38% in the under 50s and by 20% in women aged 50-69 years. The threshold for the use or otherwise of cytotoxic chemotherapy is however difficult to define and is dependent on likely benefits from treatment, co-morbidities that may make optimal chemotherapy administration difficult and patients wishes. All patients with a breast cancer should be discussed with the oncologists at the MDT who will advise on which patients should be seen by a Christie oncologist for a discussion of adjuvant chemotherapy. Such patients include those with:

- **Triple Negative Cancers (>0.5cm)**
- **Her2 Positive Cancers (>0.5cm)**

Over-expression of Her2 is an independent poor prognostic factor. The pivotal trials of adjuvant trastuzumab demonstrated a clear benefit of adjuvant trastuzumab in addition to adjuvant chemotherapy for relatively high risk breast cancers (Piccart-Gebhart 2005, Slamon 2006). There is however increasing evidence from several, albeit retrospective, studies that even sub-centimetre Her2 over-expressing breast cancers are associated with recurrence rates of 15-30% (Curigliano et al JCO27 5693-99 2009, Gonzalez-Angulo et al., JCO 2009 27 5700-6, Tovey et al., BJC 2009 100 680-3). There is no direct evidence that adjuvant chemotherapy and trastuzumab will decrease the recurrence rates among small Her2 positive cancers, but, magnitude of benefit in the adjuvant trastuzumab trials was similar across all subgroups defined by size or nodal status (Untch et al Annals Oncology 2009). Given the large magnitude of benefit of adjuvant trastuzumab plus chemotherapy (a relative risk reduction of at least 50%) chemotherapy plus trastuzumab should be considered for patients with T1b (> 0.5cm) cancers. Few women in the retrospective studies had T1a cancers and it is therefore difficult to recommend potentially toxic adjuvant therapies to women with very small Her2 positive cancers.

ER-Positive, Her2-negative Cancers

It remains difficult to define which patients with ER-positive Her2-negative should be treated with chemo-endocrine therapy. Patients who are highly endocrine sensitive may gain little from the addition of chemotherapy; such patients cannot however be easily identified and at the present time patients with an intermediate or high risk endocrine receptor positive cancer should be considered for chemotherapy. The 2009 St Gallen International Expert Consensus [Goldhirsch 2009] made the following suggestions:

	Relative Indications for Chemo-endocrine Therapy	Factors Not Useful	Relative Indications for endocrine therapy alone
ER/PgR	< 50% of tumour cells for either receptor		High ER/PgR
Histological Grade	III	II	I
Proliferation	High (>30%)	Intermediate (16-30%)	Low (<15%)
Nodes	4 or more	1-3 nodes	Node negative
LVI	Present		
Tumour size	>5cm	2-5cm	2cm
Patient Preference	Use of all options		Avoidance of side-effects

All patients, therefore, with relative indications for chemo-endocrine therapy should be considered, in the absence of significant co-morbidities, for adjuvant chemotherapy and be referred through to oncologists at The Christie for a discussion about the potential benefits and potential risks of treatment. Patients with an estimated chemotherapy benefit of greater than 4-5% for overall survival at 10 years are generally recommended adjuvant chemotherapy; patients with a potential benefit of 2-4% should be referred for a discussion though not all patients would decide to have chemotherapy for these benefits. It is important, then, that patients are informed that the referral is to discuss adjuvant chemotherapy NOT that they are being referred to have adjuvant chemotherapy.

Adjuvant Chemotherapy regimens

Anthracycline-containing regimens

The optimum anthracycline regimen is uncertain. Both the number of cycles and the total dose appear to be important. Based on the results of a number of large clinical trials, certain conclusions can be drawn.

- 4 cycles of AC are equivalent to classical CMF [Fisher 1990, Fisher 2001].
- 6-8 cycle anthracycline-containing regimens are superior to CMF [EBCTCG 1998, Levine 2005, Hutchins 2005]
- FEC 100 is superior to FEC 50 [Bonnetterre 2001].
- Regimens containing less than 240 mg/m² of anthracycline are inferior to higher doses of anthracycline [Budman 1998].

Suggested standard adjuvant anthracycline-containing regimens: EC, FEC₆₀, FEC₁₀₀, AC or Epi-CMF.

Given the potentially serious and unpredictable nature of anthracycline-induced cardiotoxicity, it is good practice to formally assess cardiac function prior to commencement of treatment, or as soon as practicably possible following commencement of treatment.

Taxane-containing regimens

Taxane-containing regimens have been extensively trialled in the adjuvant setting and been shown to provide a modest improvement in DFS and OS in some trials compared with non-taxane containing regimens [Martin 2005, Roche 2004]. They may be considered for patients with node positive disease or those who are assessed to be at high risk of recurrence due to adverse biological features.

Taxotere (Docetaxel) has NICE approval for use in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node positive breast cancer.

Options for adjuvant taxane-containing regimens include:

- 3FEC₁₀₀ followed by 3Taxotere₁₀₀ (as in the PACS 01 study).
- 4FEC₆₀ followed by 4 Taxotere
- 4EC followed by 4 Taxotere

Where anthracycline containing regimens are not considered appropriate (patients with a cardiac history or previously treated with anthracyclines) then 6 cycles of Taxotere₇₅ plus Cyclophosphamide₆₀₀ may be considered.

The TCH regimen (Taxotere, Carboplatin and Herceptin) may be considered in patients with node-positive or high-risk node-negative HER-2 over-expressing cancers. This was demonstrated in the BCIRG 006 study to have similar efficacy to AC -> TH but with less cardiotoxicity [Slamon 2006].

G-CSF prophylaxis

Primary prophylaxis may be considered in

- Selected patients in whom there are co-morbid factors which significantly increase their risk of, and from, developing a neutropenic event.
- Regimens associated with moderate or high rates of neutropenic events (. 20%) eg. FEC-T, FEC₁₀₀.

The following G-CSF regimens can be used for primary prophylaxis

- Filgrastim (neupogen)300 mcg (<70kg) or 480 mcg (>70kg) sc daily for 5-7 days
- Pegfilgrastim (neulasta) 6 mg sc single dose administered 24 hours after chemotherapy (FEC₁₀₀ or FEC-T only)

Secondary prophylaxis is indicated for any chemotherapy regimen where patients have experienced a neutropenic event from a prior cycle of chemotherapy.

Chemotherapy Toxicities

Modern chemotherapy regimens are anthracycline-based (epirubicin or doxorubicin) with the addition of a taxane (docetaxel or paclitaxel) for higher risk cancers, usually 6-8 cycles with each cycle being given every 3 weeks e.g. FEC (FEC: 5-fluorouracil, epirubicin and cyclophosphamide) or FEC-T (T = docetaxel).

The most important short term toxicity is myelosuppression with the risk of potentially fatal neutropenic sepsis. All patients who commence on chemotherapy are told to contact the Christie Hospital Hotline (0161 446 3568) as a matter of urgency if they develop symptoms of infection. Prompt treatment with broad spectrum intravenous antibiotics is indicated for febrile neutropenic patients who, untreated, are at risk of overwhelming sepsis.

Other side effects of chemotherapy include hair loss, nausea and vomiting, diarrhoea and constipation, mucositis and lethargy. Taxane based regimens tend to be more toxic with additional toxicities including myalgia and arthralgia, fluid retention, peripheral neuropathy and nail dystrophy. There is a small excess risk of cardiac toxicity and second cancers for patients who have received adjuvant chemotherapy compared to age-matched controls.

Taxane reactions

Both commonly used taxanes, docetaxel and paclitaxel are known to induce hypersensitivity reactions (HSR). The introduction of prophylactic premedication regimens for both agents has led to significant reduction in the incidence of HSR although severe HSR are seen in 1-2% of patients treated with paclitaxel despite premedication with glucocorticoids and antihistamines (H1 and H2). Nearly 80% of such reactions occur with the first dose administered and almost all within the first 10 minutes of infusion, with as little as 1mg of the drug delivered.

Adjuvant Trastuzumab (Herceptin®)

There is evidence from large clinical trials that the use of trastuzumab in the adjuvant setting significantly improves disease free and overall survival in women with HER-2 overexpressing tumours [Piccart-Gebhart 2005, Romond 2005]. The majority of studies have studied 1 year of treatment although a small Finnish study demonstrated similarly beneficial hazard ratios in DFS and OS with a nine week course given with chemotherapy [Joensuu 2006]. Adjuvant trastuzumab is indicated for women whose primary breast cancer is larger than 1cm and whose cancer is scored as 3+ by immunohistochemistry or is amplified by FISH (ratio > 2.0). Trastuzumab is given sequentially to anthracycline-based chemotherapy though appears more effective when given concurrently with taxane-based chemotherapy [Perez 2009]. There is no data to support the administration of adjuvant trastuzumab in the absence of adjuvant chemotherapy.

The recommended loading dose is 8mg/kg over 90 mins, followed by a 3 weekly maintenance dose of 6mg/kg over 90 mins, to a total of 18 doses. Following the loading dose the patient should be monitored for 6 hours for infusion-related reactions. Emergency equipment must be available. Paracetamol and antihistamines may be used to alleviate infusion-related symptoms.

Re-loading is required if there is a gap between consecutive treatments of over 4 weeks.

Where trastuzumab is used with taxane-containing regimens (eg FEC-T), the trastuzumab should be given concurrently with the taxane, rather than on completion of chemotherapy.

Cardiac health and adjuvant therapy (based on NCRI guidelines 2008)

Cardiac monitoring for patients receiving adjuvant trastuzumab

LVEF should be assessed (by Echo or MUGA) at the following time points:

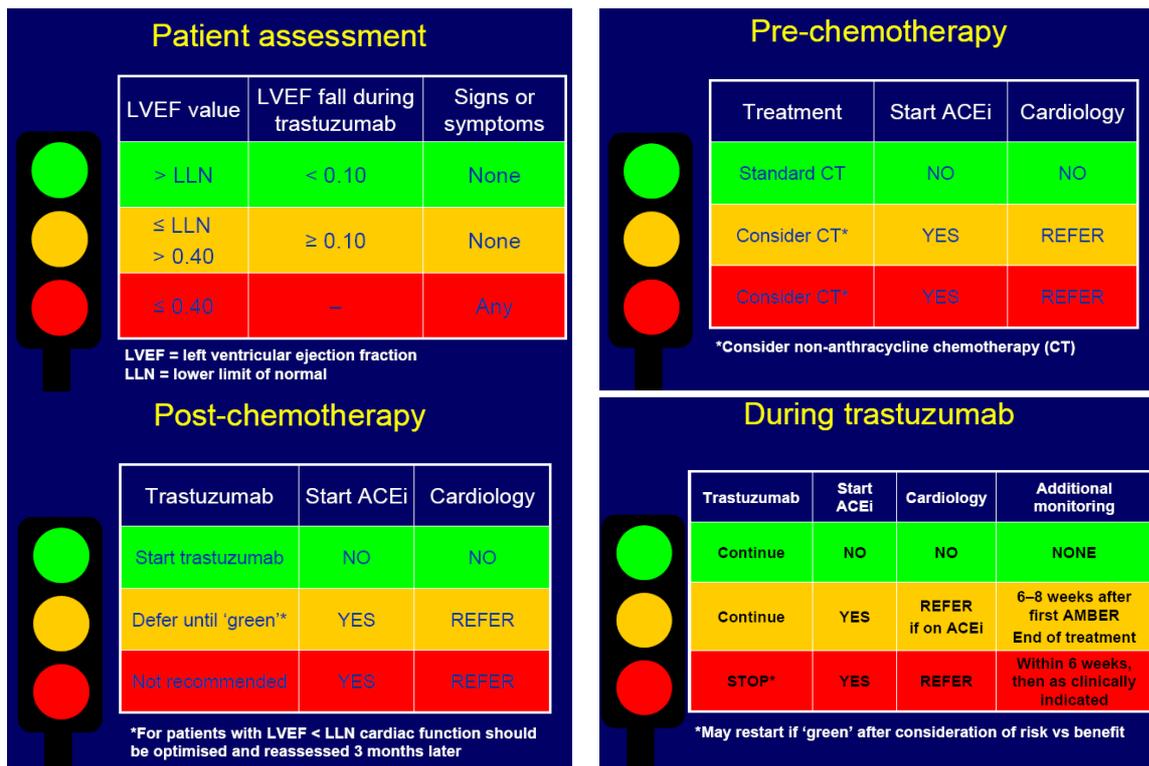
- Before chemotherapy is initiated, to establish baseline cardiac status.

- Before initiation of trastuzumab therapy, to assess the impact of chemotherapy on cardiac function, and ensure eligibility for treatment.
- After 4 months of trastuzumab therapy.
- After 8 months of trastuzumab therapy, for patients who do not experience significant changes in LVEF.
- An additional assessment should be performed at 12 months for patients who required intervention during treatment.

7.7.1.2 Recommendations for initiating, interrupting and discontinuing trastuzumab therapy

- LVEF should be greater than the local LLN before initiating trastuzumab therapy.
 - Intervention with an ACE inhibitor after chemotherapy may be necessary to achieve this. (NB DR Simon Ray (Cardiologist from SMUTH) recommends Ramipril plus Bisoprolol).
- If LVEF falls by ≥ 0.10 from the pre-trastuzumab LVEF value or to \leq LLN, initiate ACE inhibitor therapy and re-monitor after 6 weeks.
- If LVEF falls to < 0.40 or the patient develops signs or symptoms of heart failure, trastuzumab therapy should be interrupted and they should be referred to a cardiologist.
- If LVEF is restored to $>$ LLN, the patient may be re-challenged with trastuzumab, otherwise discontinue therapy.

Traffic light system to prevent, monitor and manage cardiac events before and after chemotherapy, and during trastuzumab treatment.



Recommendations for the management of hypertension in patients with breast cancer

- Patients who are diagnosed with raised blood pressure ($>140/85$ mmHg) prior to, or during, potentially cardiotoxic chemotherapy, should be initiated on an ACE inhibitor.
- Chemotherapy should not be stopped or delayed.

- Blood pressure and renal function should be monitored and ACE inhibitor dose titrated in primary care along standard guidelines.
- ACE inhibitors should be continued indefinitely, unless a contraindication occurs.
- A cardiologist should be consulted before changing or discontinuing therapy

ADJUVANT ENDOCRINE THERAPY

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 8, p38 - 46)

Endocrine treatments are as important as chemotherapy in premenopausal women and even more so in those who are postmenopausal. Anti-estrogen treatment should be reserved for women with estrogen receptor (ER) positive breast cancer (see below for classification) and considered for rare cases that are ER negative but progesterone receptor (PR) positive. Meta-analyses by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) have demonstrated that 5 years of adjuvant tamoxifen reduces the annual risk of breast cancer death by 31% irrespective of age, chemotherapy use or tumour stage [EBCTCG 2005]. Importantly this improvement in outlook is largely additive to the risk reducing effects of chemotherapy and a middle-aged woman with ER positive breast cancer will have her chances of dying from BC reduced by 50% by the use of anthracycline containing chemotherapy followed by tamoxifen [EBCTCG 2005]. Endocrine therapy should not be given concurrently with or prior to cytotoxic chemotherapy unless part of a prospective clinical trial.

Assessment of ER status

ER and PR status should be measured on all patients with invasive breast cancer at diagnosis to ensure appropriate use of endocrine treatments, which should not be used when both ER and PR are negative. International guidelines suggest endocrine therapy should be considered for any ER staining in the tumour and in practice this equates to 1% or more of cancer cells. Staining intensity is also important and the combination of proportion and intensity are now commonly combined to produce the pathological 'quick score' accordingly:

Proportion	Score	Staining Intensity	Score
0	0	none	0
<1%	1	Weak	1
1-<10%	2	Intermediate	2
10-<33%	3	Strong	3
33-<66%	4		
≥66%	5		

Proportion and intensity scores are added to derive a total score from 0-8 (1 is not possible). Tumours with scores of 0 and 2 are considered ER negative but **scores of 3 and above should be considered for endocrine therapy** [Harvey 1999]. Lower ER scores (3-6) make endocrine responsiveness less certain, worsen the prognosis and are a relative indication for chemotherapy [Goldhirsch 2007, Dowsett 2008]. In contrast quick scores of 7 or 8 are a relative indication for endocrine therapy alone.

Premenopausal women

Tamoxifen remains the mainstay of adjuvant endocrine therapy for premenopausal women and should be given for a period of 5 years [EBCTCG 2005, Goldhirsch 2007, Carlson 2009]. In women at moderate to high risk of relapse who decline adjuvant chemotherapy, ovarian suppression (OS) with goserelin for a period of 2-3 years can be considered. However, this approach is not to be recommended to any patient as a way of avoiding the toxicities of chemotherapy for the following reasons:

1. meta-analysis has demonstrated only marginal benefits over tamoxifen alone [Cuzick 2007].

2. meta-analysis demonstrating equivalence of OS to chemotherapy examined trials of older less-effective CMF based chemotherapy regimens [Cuzick 2007].
3. the effects of tamoxifen and chemotherapy are additive [EBCTCG 2005].

In younger premenopausal women (<~40 years) with moderate to high risk tumours who do not develop amenorrhoea with chemotherapy ovarian suppression for 2 years can be considered but this does not constitute level I evidence [Davidson 2005]. Data presented recently from the ZIPP trial suggest that there is no benefit to the addition of OS to tamoxifen alone {SABCS 2010}. The toxicities of this approach are likely to be severe and many women who commence combined therapy cannot tolerate it due to the intensity of menopausal symptoms.

In women in whom tamoxifen is contraindicated (usually due to a recent history of venous thromboembolism) the combination of a third generation aromatase inhibitor (AI; letrozole, anastrozole or exemestane) and OS should be considered. Such therapy has recently been demonstrated as equivalent to a combination of OS and tamoxifen in a prospective phase III randomised trial [Gnant 2009].

In women with very low risk cancers (NPI VGP group score <2.4) adjuvant endocrine therapy may be withheld after discussion of the risk/benefit ratio with the patient. This is particularly the case for pure tubular cancers which have demonstrated an almost non-existent propensity to relapse or metastasise even in the absence of systemic therapy [Rakha 2010].

Women who develop amenorrhoea whilst on tamoxifen can be considered for extended adjuvant therapy with letrozole although this should be approached cautiously [Goss 2005]; see below.

Drug interactions thought previously to reduce the effectiveness of tamoxifen

The cytochrome P450 enzyme, CYP2D6 is the rate-limiting step in the conversion of tamoxifen to its most active metabolite, endoxifen. In some retrospective studies, drugs that are known to inhibit the enzyme activity of CYP2D6, such as the antidepressants fluoxetine and paroxetine, had been shown to result in an increase in the relapse rate in patients on adjuvant tamoxifen. However, retrospective analysis of large scale randomised phase III trials (ATAC and BIG 1-98) did not substantiate these findings. These guidelines have thus been changed to reflect this and the co-prescription of such drugs is no longer felt to be contra-indicated.

Ovarian Ablation

Ovarian ablation can be achieved by LHRH analogues. Eg. Goserelin (Zoladex) 3.6 mg s.c. every 4 weeks.

There is evidence from a number of randomised clinical trials that ovarian ablation is as effective as CMF in hormone receptor positive pre-menopausal woman. However there are no trials comparing ovarian ablation to anthracycline-containing regimens which are the current standard adjuvant treatment. Ovarian ablation can be considered as an alternative to chemotherapy in patients who have good-intermediate risk breast cancer.

Whether there is an additive effect when ovarian ablation is given in addition to chemotherapy or to tamoxifen is the subject of ongoing clinical research.

There is indirect evidence from clinical trials that women who continue to menstruate after completion of adjuvant chemotherapy may benefit from ovarian ablation. The pros and cons of this approach should be discussed with the patient based on the individual circumstances.

Women who develop amenorrhoea on chemotherapy (or tamoxifen)

A cautious approach should be adopted in women who develop amenorrhoea during treatment with cytotoxic chemotherapy as residual ovarian function may persist or indeed reappear several years later. The younger the patient, the more likely this is to happen. In addition, amenorrhoea on tamoxifen is not diagnostic of postmenopausal status as tamoxifen suppresses menstruation [Smith 2006, Clemons 2007].

Prior to commencing endocrine therapy blood should be drawn for measurement of serum estradiol and FSH. It is recommended that all such women be commenced on tamoxifen in the first instance and if a sequence strategy is planned with an AI (see below) then bloods should be taken every 3 months for the first year to ensure estradiol and FSH remain in the postmenopausal ranges (high sensitivity estradiol assays are not available in Manchester). If menstruation resumes or hot flushes abate suddenly then the AI should be stopped and tamoxifen reinstated.

Post-menopausal women

Aromatase Inhibitors

Aromatase inhibitors (AIs) block the aromatase enzyme, which converts androgens produced by the adrenal glands to estrogens in abdominal fat, muscle and tumour cells. There are three AIs currently in widespread use; anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin) and over 27,000 women have been randomised in adjuvant trials of various designs to test the activity of the AIs against tamoxifen [Baum 2002, Ingle 2005, Jonat 2006, Coombes 2007, Mouridsen 2009].

Choice of endocrine therapy in the post-menopausal woman

Five years of an AI versus tamoxifen has shown improvements in disease free survival by 4% but no significant improvement in breast cancer specific or overall survival [Dowsett 2009] The majority of the benefit appears to be in the first 2-3 years of treatment and the challenge remains to identify the women who would likely benefit most from an AI. To date there is some evidence that certain tumour characteristics (large tumour size, node positivity, lymphovascular invasion and high Ki67) may be associated with increased benefit from an upfront AI treatment strategy as such tumours have a greater peak of relapse during the first 2-3 years of therapy [Mauriac 2007, Viale 2008]. For women who have received 2-3 years of tamoxifen, switching to an AI to complete 5 years of therapy does result in small but statistically significant reductions in overall [Jonat 2006, Coombes 2007] and the sequence strategy has not been demonstrated to be inferior to 5 years of an AI [Mouridsen2009].

Ongoing follow up and other clinical trials may help to define the precise timing, duration, and sequencing of endocrine therapy, in addition to the long-term tolerability profile and the potential differences between anastrozole, letrozole, and exemestane. Uncertainties remain regarding the long-term effect of oestrogen deprivation, particularly with respect to bone and lipid metabolism and these issues should be discussed with the patient.

For the majority of post-menopausal women with newly diagnosed early breast cancer an aromatase inhibitor should form part of their adjuvant management, either

- upfront for 5 years (anastrozole 1mg daily or letrozole 2.5 mg daily) or
- sequentially with 2-3 years of tamoxifen followed by 2-3 years of an aromatase inhibitor to total 5years. (exemestane 25 mg daily or anastrozole 1 mg daily)

There is no direct evidence from clinical trials to favour one of these approaches over the other in terms of efficacy. However, there is increasing evidence that certain tumour characteristics (grade 3, node positive, >5cm, or ER poor) are associated with a significant risk of recurrence within the first 2.5 years. These patients could be considered for an upfront AI, whereas tumours without these characteristics may be adequately treated by sequential use of tamoxifen and an AI, thus reducing their risk of bone morbidity.

A risk adapted strategy is therefore adopted in postmenopausal patients with ER positive breast cancers:

For women at **high risk** of relapse i.e. a NPI score >4.4 (PPG/MPG2) or women with lymph node negative cancers with adverse prognostic factors (eg large primary, high grade or Ki67 and LVI+) treatment with upfront AI for five years (anastrozole 1mg daily or letrozole 2.5 mg daily) can be considered [Baum 2002, Mouridsen 2009]. If the AI is not tolerated due to, for example, arthralgia then tamoxifen should be substituted. In patients with very high risk disease, the continuation of aromatase inhibition beyond 5 years may be considered, especially if the patient is not experiencing significant toxicities. However, there is no level 1 evidence to indicate a benefit.

For women with **low to moderate risk tumours** i.e. an NPI score of 2.4-4.4 (GPG/MPG1) a sequence strategy with 2 years of tamoxifen followed by 3 years of an AI, should be considered [Jonat 2006, Coombes 2007].

In women with **very low risk cancers** (NPI VGP group score <2.4 adjuvant endocrine therapy may be withheld completely after discussion of the risk/benefit ratio with the patient. This is particularly the case for pure tubular cancers which have demonstrated an almost non-existent propensity to relapse or metastasise even in the absence of systemic therapy [Rakha 2010]. If treatment is to be given in this group then the incremental benefits with AIs are negligible and in the absence of absolute or relative contraindications such as VTE, thrombotic CVA or obesity, five years of tamoxifen is recommended (NICE 2009).

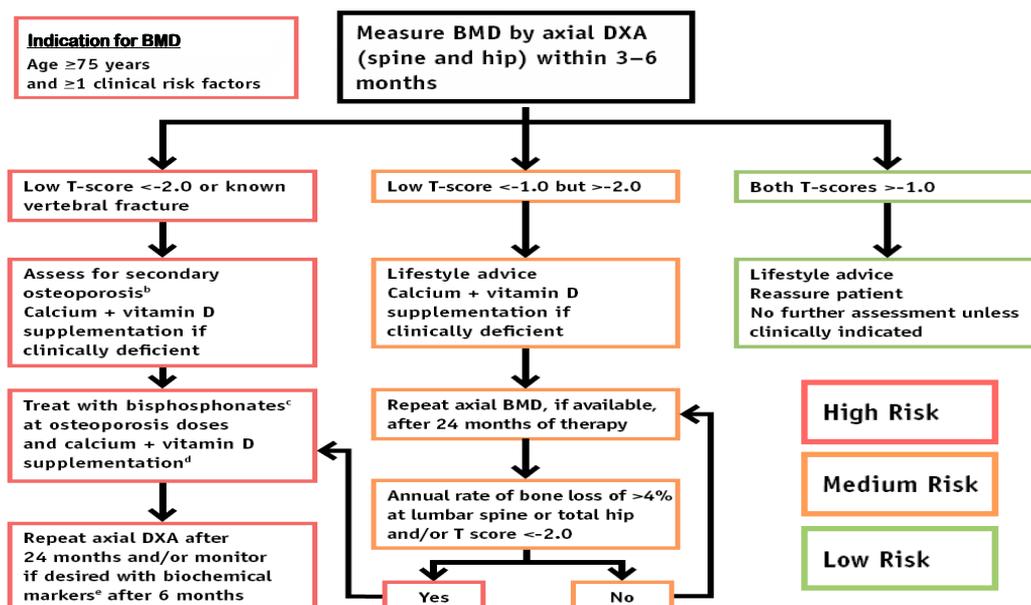
For women with node-positive breast cancers who have already received between 4.5 and 5 years of tamoxifen, the cross-over to letrozole for a further 3 to 5 years should be considered [Goss 2005]. For node negative women there is less evidence to support the use of endocrine treatment beyond 5 years. The use of extended adjuvant endocrine therapy in this situation should be based on the individual patient risk profile. More than 5 years of aromatase inhibitor use is currently not routinely recommended in any patient group.

Safety of Aromatase Inhibitors

In general AIs are well tolerated and treatment withdrawal is less frequent than that with tamoxifen. They are associated with reduced gynaecological toxicity including vaginal discharge, vaginal bleeding, hysterectomy rate and endometrial cancer. Venous thrombosis and thrombotic CVA are less common and in some studies hot flushes are less frequent although remain common.

All the aromatase inhibitors are associated with increased bone mineral loss in comparison with tamoxifen. It is accepted that this represents a combination of loss of protective effects seen with tamoxifen and an additional increased loss over baseline as a result of oestrogen deprivation. All patients starting an AI require an assessment of osteoporosis risk factors, calcium intake and baseline bone mineral density scan within three months of initiation. Bone protective therapy and subsequent monitoring should be provided according to UK consensus guidelines summarized below. AIs are also associated with an increased incidence of musculoskeletal complaints, predominately arthralgias which are occasionally severe and may require withdrawal of therapy.

Bone health and Aromatase Inhibitors (based on NCRi guidelines 2008)



The use of an aromatase inhibitor (steroidal or non-steroidal) is an indication for evaluation of BMD by DEXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DEXA before starting treatment but a baseline assessment should be obtained within 3 months of commencing an aromatase inhibitor.

Monitoring and treatment thereafter depends on the baseline BMD, age, and presence of any major risk factors for osteoporotic fracture. These are defined as:

- previous fragility fracture above the age of 50 years;
- parental history of fracture;
- a body mass index (BMI) of <22;
- alcohol consumption of 4 or more units per day;
- diseases known to increase fracture risk such as premature menopause, rheumatoid arthritis;
- ankylosing spondylitis, immobility, and Crohn's disease; and
- prior oral corticosteroid use for more than 6 months.
- For women over the age of 75 years with one or more major risk factors bone protection therapy with a bisphosphonate is recommended irrespective of baseline BMD.

For women aged under 75 years or without major risk factors, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <-2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

- Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m²) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease although intravenous bisphosphonates will usually be appropriate in such patients.
- Repeat DXA after 24 months and/or measurement of a bone resorption marker. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between -1 and -2, lifestyle advice plus calcium (1 g/day) and vitamin D (400–800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 ug/L.

- Repeat DXA scan at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <-2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

Low-Risk Group: For those patients with normal BMD (T-score >-1) the risk of developing osteoporosis over a 5-year treatment period is very low. Advice on lifestyle (diet, weight bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

- All patients should be commenced on daily oral calcium (500mg) and vitamin D supplementation (400 I.U.) and given lifestyle advice when aromatase inhibitors are started. For those patients at high risk of

osteoporosis (> 75, previous low trauma fracture after age 50, parental history of hip fracture, alcohol intake \geq 4 units/day, low BMI (<22), diseases associated with secondary osteoporosis, prior corticosteroids for > 6 months) then baseline bone mineral density (BMD) measurements are also recommended.

- The role of routine prophylactic bisphosphonate use in patients on aromatase inhibitors is the subject of ongoing clinical trials.

Bisphosphonates

Currently bisphosphonates are only indicated, in early breast cancer, for the prevention or treatment of bone mineral density loss secondary to aromatase inhibition. However, two large randomised studies (ABCSG12 and ZOFAST) have recently demonstrated significant improvements in disease free survival with early vs delayed zometa (given intravenously every 6 months for 3-5 years). The results from several other large adjuvant bisphosphonate studies are awaited, including AZURE, although preliminary results from this study demonstrate a doubling of pCR rates in the neo-adjuvant setting when iv zometa is added to neoadjuvant chemotherapy. Full publication and more mature results are required from these studies to determine whether there will be an overall survival advantage with bisphosphonate therapy and to better define the subgroups most likely to benefit

Premature ovarian failure and bone health (NCRI guidelines 2008)

- Premature ovarian failure is associated with accelerated bone loss. Tamoxifen in pre-menopausal women may increase bone loss. Women at risk should be given lifestyle guidelines to reduce their risk of developing osteopenia (stop smoking, maintain ideal BMI, regular weight bearing exercise, limit alcohol intake, and healthy diet including adequate calcium intake).
- The development of a treatment-induced menopause or planned ovarian suppression treatment before the age of 45 years are indications for evaluation of BMD by DXA. A baseline assessment should be obtained within 3 months of commencing ovarian suppression therapy or oophorectomy and within 12 months of developing post-chemotherapy amenorrhoea.
- Monitoring and treatment thereafter depends on the baseline BMD and the type of any concomitant endocrine treatment. Due to the very rapid bone loss observed with the use of ovarian suppression therapy plus an aromatase inhibitor, a different threshold for follow-up, monitoring and intervention is recommended.
- Any patient with a documented vertebral fragility fracture or previous low trauma hip fracture should receive prophylactic bisphosphonate treatment irrespective of baseline BMD.

Recommendations

- Patients with low risk tumours (NPI < 2.4) may be offered tamoxifen for 5 yrs.
- Pre-menopausal patients should be offered tamoxifen until menopause has been biochemically confirmed. Extended adjuvant therapy with letrozole may be considered if grade 3.
- Peri-menopausal patients should be offered planned switching (when menopausal) (using exemestane or anastrozole)
- Her 2 +ve does not impact on choice of endocrine therapy
- All post-menopausal patients (except low risk) should be offered an AI upfront (letrozole or anastrozole) (efficacy and cost are very similar; hence clinician preference). Normal duration is 5 years.
- Side effect management; at the time of starting an AI a DEXA scan should be undertaken. calcium /vitamin D supplement MAY BE co-prescribed if patient is deficient.
- The scan should be repeated according to national guidance once the BMD has been determined.
- Management of treatment induced bone loss as per national OS guidelines
- Node positive patients show benefit with initial therapy using an aromatase inhibitor (letrozole) (BIG 1-98) adjuvant use of hormonal therapy following 5 years of an aromatase inhibitor.

CLINICAL RESEARCH

Every Trust in the Network delivering breast cancer treatments is actively involved in clinical research. Annually, the CSG agrees a portfolio of trials and studies in which GMCCN patients can participate. Each MDT then also agrees to this list. A quarterly update of trial recruitment is provided Greater Manchester & Cheshire Cancer Research Network (GMCCRN) and discussed at each CSG meeting. A summary of the recruitment, from April to the following March, by each breast team is produced by GMCCRN. Based on these figures, each MDT produces a programme for improving trial recruitment.

At all stages of their journey, breast cancer patients should be considered for clinical trials and studies and all eligible patients should be given the opportunity to take part. Patients should be considered for referral to other Trusts for clinical trials when no suitable trials are available locally.

Breast teams in GMCCN are committed to supporting approved clinical trials and other well designed studies. In recent years GMCCN has been the top recruiter to breast cancer trials in the country. It is the intention of the Breast CSG to maintain this position.

For contact details of local Research Nurses in each Trust, please contact the GMCCRN office on 0161 918 7414

The GMCCRN Research Manager for Breast Cancer Trials is Dr Zoe Coombe (0161 918 7356)

SPECIAL CLINICAL SITUATIONS (CHRISTIE GUIDELINES SECTION 4 P14-15)

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 4, p13 - 16)

There are a number of special situations encountered in patients with breast cancer that need individualised management.

Lymphoedema

Lymphoedema may develop as a result of metastatic disease in the axilla or as treatment related either from surgery or radiotherapy. Disease may not be palpable in the axilla and MR imaging can provide useful information as the most likely cause of lymphoedema. When lymphoedema is disease related the use of radiotherapy or drug therapy should be considered. Patients who develop lymphoedema should be referred to the lymphoedema specialist for appropriate management which may involve massage, exercises, simple lymphatic drainage or manual lymph drainage, support/compression with graduated compression hosiery or multi-layer bandaging, and skin care. All women undergoing axillary node clearance should have their arm circumference measured with a tape or perometer at 4 cm intervals, prior to surgery, in line with national guidelines

Brachial plexus neuropathy

Radiation induced brachial plexus neuropathy is seen here only extremely rarely, as result of the radiotherapy techniques the Christie uses. The RAGE group was formed in the 1990's by patients suffering injury following treatment at some other units and there is a specific RCR report and guidance on this. The department has nominated Dr Magee to investigate any patient referred with this suspected problem.

Whatever the aetiology, affected patients usually have difficult neuropathic pain, progressive loss of function and may also develop lymphoedema. Consider referral to the local pain clinic or specialist palliative care (the latter may prove easier to access) for advice with pain management. Hospices often provide lymphoedema care also. Occupational therapy assessment should be requested as early as possible for consideration of splints, practical advice and aids to help adaptation to disability.

Pregnancy associated breast cancer

- Patients who present in the first trimester of pregnancy should be considered for therapeutic termination since radiotherapy and the majority of cytotoxic drugs are potentially damaging to the foetus.
- Patients presenting later in pregnancy should be treated by means of mastectomy and delivered as early as considered feasible by the Obstetrician (usually 32-34 weeks).
- The use of chemotherapy during the 2nd and 3rd trimester has been shown in small studies to be relatively safe to both the mother and the foetus [Ring 2005, Giacalone 1999, Berry 1999]. However, long-term effects on the unborn child are not yet known and its use should be approached with caution.
- Chemotherapy can usually be safely commenced around 2 weeks following delivery as long as there are no post-operative wound complications.
- Patients should be advised not to breast-feed while on chemotherapy.
- Thereafter the patient should be treated in the same manner as a non-pregnant patient. High risk patients are advised not to become pregnant for at least 2 years after completing treatment, as this is the time of highest risk of recurrence. Population-based studies have shown that pregnancy following a diagnosis of breast cancer is not detrimental to survival [Velentgas 1999, Sankila 1994].

Female fertility preservation

Adjuvant chemotherapy in pre-menopausal women risks premature ovarian failure and infertility. Women who are under 40 at the time of their diagnosis and who have not yet completed their family are entitled to a referral to the GMCCN female fertility service to discuss fertility options which include ovarian stimulation and embryo storage prior to adjuvant chemotherapy. Such women should be referred to the fertility service **at the time of their diagnosis in order to allow sufficient time for fertility preservation techniques** even if the need for adjuvant chemotherapy is uncertain at the time.

Whilst all premenopausal women are entitled to have the option of discussing fertility issues and options, fertility treatment will only be funded within current NHS guidelines, for example, women under 40 years. Women older than 40 years may still be referred for a consultation, however, if they decide to pursue fertility preservation options, private care will be recommended.

To refer a patient for a consultation, please download and complete '**URGENT REFERRAL FOR FERTILITY CONSULTATION**' form from the Greater Manchester and Cheshire Cancer Network website and fax directly to Dr Cheryl Fitzgerald on 0161 224 0957. Patients will be contacted within an appointment and seen within 7 working days.

Women with concerns about fertility preservation may also be referred for a consultation to one of two breast oncologists to discuss the oncological aspects of fertility preservation. For patients in North Manchester area: Dr Juliette Lancaster. For patients in South Manchester area: Dr Anne Armstrong. The referral can be for consultation only or for breast cancer treatment and ongoing care, and should be sent off at the same time as the referral to St.Mary's, at the time of diagnosis.

Adjuvant rather than neoadjuvant chemotherapy may be more appropriate for many women who are concerned about fertility preservation.

Menopausal symptoms

Hot flushes frequently occur in breast cancer patients as a result of a treatment-induced premature menopause or as a side effect of treatment. Patients often prefer to take non-prescription treatments such as Evening Primrose oil, Vitamin E or Red clover. Randomised studies have indicated that these remedies have a 20-25% likelihood of benefit, which is similar to that of placebo [North American Menopause Society 2004]. These options may be a reasonable first option for some patients with mild symptoms who wish to avoid prescription drugs. However, if flushes and sweats are troublesome and persistent, then venlafaxine 37.5 mg can be used, but it should be noted that venlafaxine is a weak CYP2D6 inhibitor and if the patient is already on Tamoxifen, then the potential for interaction should be considered. Please note that venlafaxine also should not be prescribed in patients with heart disease, electrolyte imbalance or hypertension.

The use of HRT after a breast cancer diagnosis is not recommended as there is no evidence from randomised controlled trials that this is safe. Oestrogen based HRT is reserved for patients with very severe symptoms despite use of other remedies. In these situations the patient must be counselled as to the potential safety concerns. It is reassuring if the primary tumour is both oestrogen and progesterone receptor negative.

Male breast cancer

Less than 1% of breast cancer occurs in men, usually in the 6th or 7th decade. Presentation is with a mass usually below the areola but there is often fixation to the underlying muscle. Following histological or cytological confirmation treatment is normally by mastectomy and axillary surgery with post-operative radiotherapy since it is difficult to obtain adequate clearance at the deep resection margin. Adjuvant Tamoxifen is also recommended. The prognosis is the same as for age and stage matched female patients.

LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 9, p47 - 48)

Definitions

Locally Advanced

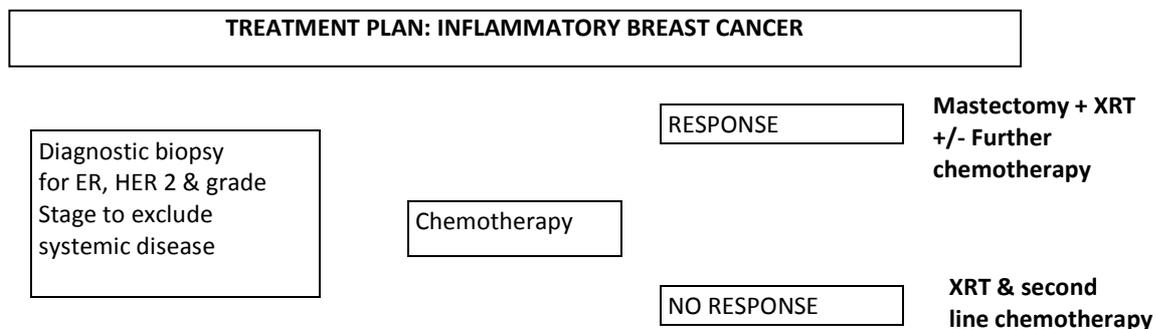
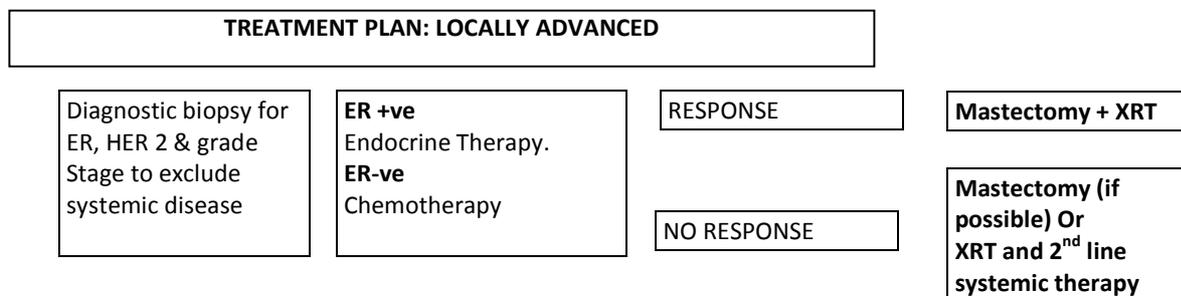
- Patients with inoperable tumours due to skin or chest wall involvement or fixed axillary nodes.
- Metastases limited to ipsilateral supra-clavicular fossa or infra-clavicular region.

Inflammatory

- A clinical diagnosis based on the presence of erythema and peau d'orange of >1/3 of the skin of the breast in a patient with a biopsy proven cancer.
- Inflammatory breast cancers are associated with very poor outcomes.
- Inflammatory carcinomas are usually ER negative and frequently are associated with HER2 over expression and p53 mutations.

Management

- Staging should be performed to exclude distant metastatic disease.
- Treatment is multi-modality. This involves either endocrine therapy (unlikely in IBC) or primary chemotherapy with anthracyclines +/- taxanes followed by mastectomy and axillary node clearance and post-operative loco-regional radiotherapy plus adjuvant endocrine therapy if ER+ve [Dawood 2010]. Trastuzumab should be incorporated into the pre-operative chemotherapy regimen in HER2 over-expressing tumours [Dawood 2020]. Response to treatment should be monitored radiologically as well as clinically during treatment.
- For information regarding clinical trials in patients with locally advanced and inflammatory breast cancer please refer to the Christie Hospital Clinical trials website.



LOCALLY RECURRENT DISEASE

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 10, p48- 49)

- In the presence of locally recurrent disease, distant metastases should be excluded
- The prognosis depends on the site of local relapse, the extent of relapse and the interval since primary treatment
- Local treatment options with surgery and radiotherapy will depend on the extent of previous treatment
- Local relapse following breast-conserving surgery is managed by a mastectomy in the majority of cases. Relapse within 2 years of primary treatment has a less good prognosis.
- An isolated relapse on the chest wall following mastectomy should be managed by wide local excision and radical radiotherapy (if not previously given). A proportion of these patients will be long-term survivors. Widespread relapse on the chest wall has a poor prognosis. Selected patients may be suitable for chest wall resection. Otherwise widespread chest wall relapse is managed with systemic therapy and palliative radiotherapy.
- Axillary relapse is managed if possible with surgery and/or XRT depending on the nature of treatment used at the time of primary treatment. Extensive inoperable disease has a poor prognosis.
- Supra-clavicular fossa relapse is managed with palliative XRT and systemic therapy
- The selection of systemic therapy is based on the principles set out in Section 9. There is limited data on the effectiveness of systemic therapy, particularly chemotherapy in this situation.
- For information regarding clinical trials in locally recurrent disease please refer to the Christie Hospital Clinical Trials website

METASTATIC BREAST CANCER

All suspected metastatic / recurrent cases should be discussed at local MDT meeting and referred to the relevant oncologist

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 11, p38 - 46)

Aims

- To palliate symptoms and maintain quality of life.
- To extend life if possible.

Management points

- Treatment options include specific systemic therapies: Endocrine therapy, chemotherapy and herceptin; supportive therapies, such as bisphosphonates; and specific local therapies; radiotherapy and surgery.
- Receptor status will guide the selection of specific systemic therapy; oestrogen and progesterone receptor estimations, HER 2 status.
- It is usual to start with endocrine therapy in ER or PR +ve patients, particularly with a long disease-free interval, but chemotherapy should be used where there is rapidly progressive lung or liver disease or early relapse on adjuvant hormone therapy.
- Although metastatic breast cancer is not curable with present treatments, specific systemic therapy is of value in the palliation of symptoms with survival advantage for those who respond to treatment.
- Appropriate expertise must be available to deal with the side effects of chemotherapy, which may be life threatening.
- Chemotherapy should be used with extreme care in elderly patients who may have other significant medical problems and cope poorly with common side effects of chemotherapy eg neutropenic sepsis.

- Explanation of the disease process and treatment plans to the patient is highly important.
- Close co-operation between the breast team, the palliative care multi-disciplinary team and the family doctor is needed to provide the best care and support for the patient and her family. Appropriate psychological support is essential.

Endocrine Therapies

In general endocrine treatment should be offered as the first option to most women with hormone-sensitive metastatic breast cancer, due to the lower toxicity of endocrine therapy and generally longer duration of response compared to cytotoxic therapies. Chemotherapy may be considered when the disease is rapidly progressing and/or life-threatening.

Post-menopausal woman

First line endocrine therapy should be a non-steroidal aromatase inhibitor

- Non-steroidal aromatase inhibitors): Anastrozole 1 mg OD, or Letrozole 2.5 mg OD.
- Steroidal aromatase inhibitors Exemestane 25 mg OD (Exemestane has some activity in patients who have failed non-steroidal aromatase inhibitors [Lonning 2000]).
- .Selective oestrogen receptor modulators: Tamoxifen 20 mg OD
- Anti-oestrogens: Fulvestrant (Falsodex) administered by monthly i.m. injections. 500mg every 4 weeks, with an additional loading dose on Day 14 of the initial cycle.
- Progestogens: Megesterol acetate 160 mg OD.

Pre-menopausal woman

First line endocrine therapy should be Tamoxifen plus ovarian ablation

- Ovarian ablation (in premenopausal patients)
 - LHRH agonists, eg. Goserelin (Zoladex) 3.6 mg every 4 weeks.
 - Radiotherapy-induced menopause
 - oophorectomy.

Chemotherapy

- The selection of chemotherapy regimen will depend on the extent and sites of metastatic disease, whether prior adjuvant chemotherapy has been given, and the likely toxicity of the regime.
- The anthracyclines (doxorubicin and epirubicin), and the taxanes (docetaxel and paclitaxel) are the most active agents. Both of these agents must be used with caution in patients with extensive liver disease.
- Patients with primary anthracycline resistance or who relapse after anthracycline-containing adjuvant therapy regimes should be considered for chemotherapy with taxanes, vinorelbine, or capecitabine, as single agents or in combination regimes.
- Consider if the patient is eligible for a clinical trial

Chemotherapy agents/regimes in the metastatic setting

- Anthracyclines: Doxorubicin, Epirubicin, FEC, EC or AC. Liposomal doxorubicin (Myocet) may be considered in patients who have previously received anthracycline where there is concern about potential cardiotoxicity.
- Taxanes: Docetaxel and paclitaxel used as single agents or in combination regimes (Docetaxel/Capecitabine or Paclitaxel/Gemcitabine). Nab-paclitaxel has been shown to be equally effective as taxotere 100 mg/m², but with reduced toxicity [William 2009]. Nab-paclitaxel can be used in place of single agent three weekly taxotere. In patients with a HER-2 receptor over-expressing tumour, nab-paclitaxel can be used in combination with trastuzumab.
- Capecitabine used as single agent or in combination regimes
- Vinorelbine (oral or iv) used as single agent or in combination regimes
- Carboplatin or Cisplatin (usually in combination with a taxane or gemcitabine).
- Gemcitabine (usually in combination with a taxane)
- CMF: cyclophosphamide, methotrexate, fluorouracil

Trastuzumab

Trastuzumab (Herceptin) is a monoclonal antibody licensed for the treatment of metastatic breast cancer. Patients are only suitable if they strongly over-express the HER 2 protein (approx 25% of patients) and the response rate for single agent trastuzumab is approx 30% [Vogel 2002].

There are 2 broad categories of trastuzumab use in metastatic breast cancer

1. Trastuzumab monotherapy.
 - (a) Patients with HER2 receptors of 3+ (immunostaining or FISH positive).
 - (b) Evaluable metastatic disease.
 - (c) Good performance status: WHO \geq 2
 - (d) Life expectancy at least 6 months.
 - (e) Disease relapsing after treatment with anthracyclines and taxanes (as per the datasheet); failed hormone therapy.
 - (f) Absence of significant cardiac disease (cardiac scan before treatment).
2. Trastuzumab in combination with chemotherapy.
 - (a) – (d) as in 1 (a) – 1 (d)
 - (e) First relapse with metastatic breast cancer
 - (f) The drug can be used in combination with taxanes, vinorelbine, or capecitabine.
 - (g) Absence of significant cardiac disease.

There is some evidence supporting the use of trastuzumab beyond progression, as a second line therapy [von Minckwitz 2008].

Lapatinib

Lapatinib plus Capecitabine increases overall survival and time to progression compared with capecitabine alone in patients with metastatic or locally advanced breast cancer that has progressed though trastuzumab [Geyer 2006].

Lapatinib 1250 mg/m² per day continuously with Capecitabine 2000 mg/m²/day in divided doses 12 hours apart, day 1-14 of a 21 day cycle

Algorithm for use of lapatinib

METASTATIC OR LOCALLY ADVANCED HER2 OVER-EXPRESSING BREAST CANCER (previous anthracycline therapy)
1ST LINE TRASTUZUMAB + TAXANE*
2ND LINE LAPATINIB + CAPECITABINE OR TRASTUZUMAB + VINOURELBINE*
3RD LINE CHEMOTHERAPY ONLY <u>STOP</u> Erb-B2/HER2 targeting therapy (unless in clinical trial)

* other chemotherapy drugs may be used if clinically appropriate

Funding is through the Cancer Drugs fund.

Bisphosphonates for patients with bone metastases

Bisphosphonates are indicated for use in patients with bone metastases. They have been demonstrated to reduce skeletal related events and symptoms resulting from bone metastases.

The preferred intravenous bisphosphonate is zoledronate (see the information sheet for its use). Oral ibandronate 50 mg daily can be prescribed as an alternative to intravenous zoledronate, and should be considered in patients who are not attending hospital clinics for intravenous chemotherapy. A shared care protocol with GPs has been devised. Oral ibandronate may also be used in patients with impaired creatinine clearance (<30) when a dose reduction to 50 mg once a week is advised.

The use of bisphosphonates has been shown to reduce the incidence of vertebral fracture and radiotherapy requirements in patients with widespread metastatic bone disease.

Rare cases of osteonecrosis (primarily of the mandible) have been reported in patients treated with bisphosphonates. The majority of cases have occurred following tooth extractions. We recommend that patients with dental problems should have any dental surgery performed prior to commencing bisphosphonates. Once treatment has been commenced, any patient requiring dental surgery should be referred to a hospital dental/maxillofacial surgeon.

Indications for radiotherapy

- Bone metastases:- pain relief (single fractions of radiotherapy are as effective as prolonged courses); as part of the management of pathological fractures; spinal cord compression.
- If symptoms of pain are widespread it is preferable to give a trial of systemic therapy before radiotherapy. Radiotherapy given to multiple sites compromises the bone marrow and may prevent the patient receiving palliative chemotherapy even when indicated.

- Troublesome tumour deposits e.g. skin or nodal deposits, choroidal metastases.
- Brain metastases:- Palliative cranial XRT can be considered for patients with reasonable performance status, minimal neurological deficit and quiescent systemic disease at other sites.

Special clinical situations in metastatic breast cancer

Malignant hypercalcaemia

Hypercalcaemia may occur in the presence of bone metastases or due to production of PTH like substances. The diagnosis should be considered in a breast cancer patient who develops thirst, polyuria, nausea, vomiting or mental confusion. Patients should be considered for treatment if $\text{Ca}^{2+} > 2.8$ mmol and/or symptomatic. They should receive i.v. bisphosphonates, after hydration with saline for correction of dehydration. Serum corrected calcium should be checked 5-7 days after treatment with bisphosphonates. Effective anti tumour treatment minimises the risk of recurrence and should be deployed where appropriate. However even patients whose disease is refractory to standard systemic therapies can be treated with intravenous bisphosphonates given every two to four weeks to maintain normal serum calcium. Hospices may be able to offer admission for treatment of hypercalcaemic episodes and this option should be considered for those with advanced disease.

Bone fractures

- Prophylactic orthopaedic surgery is recommended to prevent fracture through lytic lesions in the proximal femora and humeri, especially when a lytic lesion involves 50% or more of the cross-sectional diameter.
- Patients with metastatic bone disease may develop pathological bone fracture leading to considerable pain and morbidity. Weight bearing long bones and vertebrae are especially vulnerable and patients at risk of or with established fractures of long bones e.g. neck of femur or head of humerus should be referred
- for orthopaedic assessment. Following surgery post-operative radiotherapy should be given to include the whole length of any prosthesis present. Patients with pathological fractures at other sites such as ribs or pelvis do not require surgical intervention but often benefit from radiotherapy for pain relief and to promote healing.

Liver metastases

Usually liver metastases are treated with systemic therapy. However for very selected patients it may be

appropriate to refer for consideration of local liver therapy such as surgical resection, Radiofrequency Ablation,

Selective Internal Radiation Therapy, or intra-hepatic chemotherapy:

- good performance status
- liver disease is the disease threatening the patient's longevity
- no radiological evidence of extra-hepatic metastases which would lead to quick progression (e.g. intra-abdominal disease (such as peritoneal or nodal), pleural disease, or brain metastases or uncontrolled local disease). Controlled small volume disease of bone or lungs not complete contra-indication but is relative contra-indication..
- Previous response to chemotherapy/immunotherapy which self selects patients who are less likely to progress quickly outside the liver or very indolent disease.
- For surgery: predominantly solitary metastases (+/- close daughter lesions), with less than 6/8 of liver affected confirmed by contrast MRI scan
- For Selective Internal Radiation to the Liver (SIRT): peri-operative Oxaliplatin and 5FU (OxMdg) or Irinotecan and 5FU (IrMdg) are commonly used to enhance response and prevent extrahepatic progression."

Suggestion for patient pathway:

1. Patient identified early as liver metastases being the life threatening aspect of patient's condition. Ideally liver only disease or only small volume disease outside the liver - e.g. small volume lung or bone metastases.
2. Patients discussed at MDT at which a HBP surgeon and a Breast Oncologist are present.
 - a. Patient performance status, prognosis and response to chemo/immunotherapy discussed
 - b. Is this technically resectable?
 - c. Is SIRT or a non surgical approach an option and justified in the clinical context?
3. Contrast enhanced Liver MRI and PET-CT scan performed
4. Patient reviewed by HPB Surgeon/Oncologist and plan made.
5. Medical therapy continues in the meantime
6. Medical therapy continues peri-operatively if possible (e.g. herceptin/hormone therapy or even certain chemotherapies- e.g. capecitabine)

Neurological problems

Brain metastases.

- Patients with brain metastases may present with symptoms of raised intracranial pressure, neurological deficit, seizures or mental deterioration. Dexamethasone should be given for raised intracranial pressure pending confirmation of the diagnosis by whole brain CT scan or MRI.
- Seizures can be controlled by anti convulsants. Patients should be considered for palliative radiotherapy taking into account the status of other sites of metastatic involvement. The long term results of treating disease of the central nervous system are disappointing, most patients dying within six months, although some remain free of symptoms for a considerable period of time.
- Selected patients may be suitable for consideration of surgical excision:
 - Solitary metastasis in an accessible site
 - Stable extracranial disease
 - PS 0-1
 - Life expectancy > 6months
- Following surgical excision, whole brain radiotherapy is indicated.
- Stereotactic radiotherapy may be considered in good performance status patients with controlled extra-cranial disease and ≤ 3 intra-cranial metastases and for patients with a solitary cranial metastasis which is surgically inaccessible.
- Following stereotactic radiotherapy there is no evidence that whole brain radiotherapy improves survival.

Spinal cord compression

- MRI scan is the investigation of choice. It should be requested urgently and within 24 hours of clinical suspicion. CT scan should be requested if MRI scan is not possible (cardiac pacemaker, metal implants, severe claustrophobia).
- Imaging should be performed at the nearest local hospital and scans should accompany the patient when transferred for radiotherapy or surgery.
- High dose steroids should be commenced with clinical suspicion (dexamethasone 16 mgs. i.v/p.o immediately then 16 mgs. daily).

- When imaging confirms clinical diagnosis of cord compression, a senior clinician (specialist registrar or consultant) must refer for urgent treatment. Ideally this should be within 24 hours of onset of neurological symptoms and certainly within 24 hours of confirmation by imaging.

Indications for Radiotherapy:

- Spinal cord compression confirmed by imaging (preferably MRI)
- Following spinal surgery for spinal cord compression unless the patient has had previous radiotherapy to the same level.
- Not suitable for surgery

Relative contraindications to radiotherapy

- Cord compression is due to vertebral displacement/spinal instability
- Previous radiotherapy to same spinal site
- Poor general condition due to other major and irreversible clinical problems
- Prognosis likely to be less than 1- 2 months

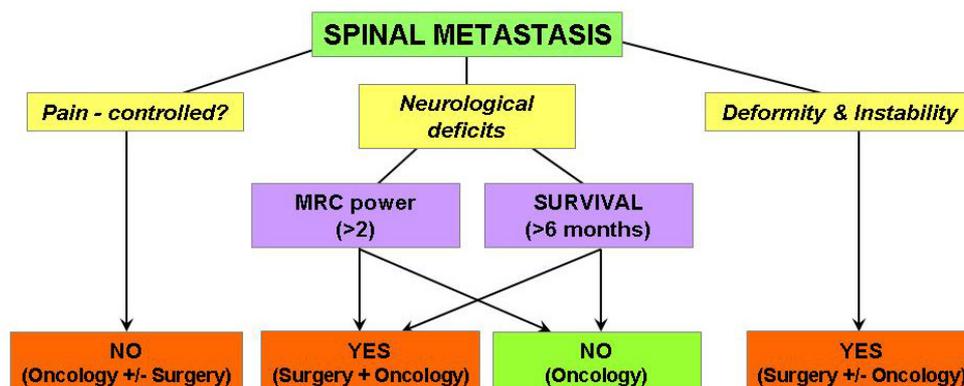
Situations when surgery should be considered

- generally limited sites of spinal involvement
- cord compression with neurological deficits
- patient is not plegic and is able to move the limb against gravity (MRC grade > 2)
- pain not responding to other measures (eg radiotherapy)
- in cases of spinal instability and/or deformity (including an opinion on spinal stability)
- patient is medically fit (for a general anaesthetic)
- patient has a **life expectancy of at least 6 months**

Early surgery (before severe neurological deficits) produces the best outcome

Surgery is best undertaken prior to radiotherapy (less risk of wound complications)

The **following referral pathway is not absolute** and when in doubt discuss with the relevant Neurosurgical and/or Spinal teams at SRFT.



SURGICAL OPINION:

Contact the on call Neurosurgical SpR (pager – 07623 617892 or via switch board – 01617897373 at SRFT)

For more information and protocols on management of spinal cord compression, see [www.christie.nhs.uk/spinal protocols](http://www.christie.nhs.uk/spinal_protocols)

SPECIALIST SERVICES

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 11, p58 - 62)

Palliative and Supportive care

Specialist Palliative Care Teams are based in community, hospital and hospice settings and work alongside both oncology and primary care teams to support the patient and family. Good communication between all professionals is essential.

When to consider referral to Palliative Care Services:

- There are persistent and troublesome pain and symptom problems
- Additional psychological support would help patient and/or family especially in the final weeks and months
- The patient/carer would benefit from specific services such as lymphoedema management, complementary therapies which are usually provided within hospices
- Help is needed to plan future care, for example
 - weekly day hospice care to monitor, support the isolated patient or give carers "time out"
 - in-patient hospice care for symptom control, rehabilitation, terminal care
 - "respite": planned, short term (usually 2 weeks) hospice stay which may provide intermediate care between hospital and home, or give families a break

Early opportunities to enable the patient to have contact with palliative care should be used as this enables links to be made between the terminal phase and helps to avoid crisis situations.

Palliative care advice to professionals is available through a helpline at St. Ann's Hospice (0880 970 7970).

Pain Specialist Teams

These are hospital based and provide out-patient clinic services. Often pain associated with active, progressing cancer is managed by palliative care specialists as there are often multiple co-existent problems; however pain specialists provide valuable advice and help for those with difficult and intractable pain. Referral to a chronic pain service may be appropriate for those patients who are cured of their cancer but live with difficult pain as a result of treatment or the disease. Often this management requires a multidisciplinary approach in which the focus has moved from the cancer itself to rehabilitation.

Specialist Psychological Support

- Patients and carers with difficulties in the following areas might benefit from some form of psychological support.
 - Anxiety
 - Depression
 - Personal relationships
 - Psycho-sexual problems
 - Alcohol and substance misuse
 - Past psychotic illness
 - Organic brain disorders
- It is the responsibility of all health care professionals to be aware of psychological concerns and refer on where appropriate.
- In most cases where psychological concerns are identified it is reasonable to initially refer to the breast care nurse/clinical nurse specialist.

- The Breast Care nurse should assess the patient and appropriately refer on for further psychological support, either to the Psycho oncology service at Christie hospital, or possibly to local services, such as primary care or local Macmillan centres or hospices.
- Liaison should be maintained with Mental Health Teams for those patients with co-morbidity.
- (NICE Supportive and Palliative Care Guidance)

Breast Cancer Nurse Specialists

All patients with breast cancer should have access to a named Breast Clinical Nurse Specialist (CNS) to support them throughout diagnosis, treatment and follow-up care (NICE 2009, NCAT 2011). The CNS will usually be their Key Worker (NCAT 2011). This reflects the growing evidence that coordinated care provided by CNSs can deliver better outcomes for patients (DOH 2011).

CNSs should be proficient in screening for psychological distress and providing basic psychological interventions. Approximately 50% of patients with cancer experience levels of anxiety and depression severe enough to adversely affect their quality of life, and a third report significant levels of distress well after treatment has been completed (Macmillan 2011). Patients and carers value the emotional and psychological support they receive from CNSs (RCN & BCC 2004).

To comply with the Peer Review requirement to provide level 2 psychological support, at least one member of the MDT needs to have completed additional training, and receive monthly clinical supervision by a level 3 or 4 practitioner (NCAT 2011). The training comprises attendance on the National Advanced Communications Skills Training course plus an accredited network based psychological training programme.

A review of the CNS role by GMCCN Lead Nursing Group (Barlow et al May 2011) has shown the high degree of clinical expertise, innovation, leadership and continuity of care brought to patients. Whilst it is acknowledged that roles vary greatly, CNSs are taking on additional responsibilities, such as follow up care, initiating clinical investigations, diagnosis, treatment decision making, management and prescribing.

Cancer is increasingly an illness which may be cured or may be a long term condition that people live with for many years. Therefore survivorship has become increasingly important as individuals are encouraged to look forward after treatment has been completed to enable them to lead as healthy and active a life as possible. Breast CNSs therefore have an important role in educating and empowering people in line with the National Cancer Survivorship Initiative (DOH 2011)

GMCCRN Research Nursing Team

Research nurses in each acute Trust. Contact via GMCCRN 0161 918 7414

Lymphoedema Services

Lymphoedema services are currently available, although limited in certain areas, through the following:

- Local Breast Care Nurses
- Christie Hospital (contact: Mrs. Liz Jordan or Paula Williams, Lymphoedema Specialists)
- See Greater Manchester and Cheshire Cancer Network website for information about local services
- Out of area services may be found through the British Lymphology Website <http://www.thebls.com>

Physiotherapy

All patients having treatment for breast cancer should have access to physiotherapy at the following stages of the treatment journey:

- Patients undergoing surgery should be taught specifically designed exercises and receive advice regarding lymphoedema prevention.
- Patients should be followed up in post-operative clinics to ensure that full movement is regained and if problems arise, patients should have access to specialist out-patient physiotherapy to prevent chronic problems with pain and dysfunction.
- Patients due to undergo radiotherapy should be invited to attend an exercise class where instructions are given on the appropriate exercises necessary to maintain shoulder movement during and after radiotherapy.
- Patients who present with lymphoedema, impaired shoulder movement and pain, muscle weakness, cording in the arm/axilla, headaches, neck and back pain and postural problems should be referred for specialist out-patient physiotherapy.
- Patients with metastatic disease who develop problems with pain and reduced mobility.

Complementary Therapies

These services are provided in local settings by voluntary agencies such as Beechwood Cancer Care (Stockport), Neil Cliffe Centre (Wythenshawe Hospital) and many hospices. Information about complementary therapies available to outpatients may be accessed through the Cancer Information Services.

Complementary services are also available at the Christie for inpatients and those coming in daily for treatment. These services are free to the patient and include massage, aromatherapy, chair massage, relaxation techniques and the Snoezelen Room. Smoking cessation advice is also available for patients and carers.

Relaxation classes are held in the Rehabilitation Unit on Tues and Thurs at 6.30-7.15pm.

For further information regarding complementary therapies please contact Peter Mackereth (Complimentary Therapy Co-ordinator) 0161 446 8236.

FOLLOW-UP AFTER BREAST CANCER TREATMENT

- Asymptomatic breast cancer patients will be followed up by a surgical team (when adjuvant chemotherapy and radiotherapy are completed)
- Follow up for breast cancer should be stratified according to risk and agreed at MDT meeting
- Patients should be seen after the first year; and years 2 and 3. If patient is ER positive, they should be seen at 5 years to stop adjuvant treatment, as per NICE guidance.
- Routine clinical follow up should be no longer than 5 years unless patients are in clinical trials
- Routine follow up may be undertaken by any specialist health care professional
- At the start of primary treatment, the patient should be provided with a written care plan.
- Patients should have a contact number for the specialist breast cancer nurse whom they can contact for advice.
- Patients should have continued access to Breast Care Nurses. Further outpatient consultations may be arranged as necessary by the breast Care nurse.
- Mammographic follow up is for at least 5 years. Patients aged <47 after 5 years follow-up should carry on with annual surveillance until they enter the NHS BSP
- Local protocols should be agreed for recall arrangements for imaging follow-up and access to specialist clinics following discharge from clinical surveillance.

3 types of follow-up:

Clinical (surgical & oncological)

- monitor adjuvant endocrine therapy
- assess cosmetic outcome
- duration & frequency of visits as per local protocol and risk stratified
- note poor evidence for over frequent clinical follow-up

Mammographic

- risk stratified as per local protocol
- NICE recommends annual follow-up to 47years then discharge to NHS BSP if patients is more than 47years old at diagnosis
- If patient is younger than 47 years after 5 years of mammographic surveillance, then continue annual mammograms until she reaches 47 years then discharge to NHS BSP

Survivorship

- BCN or AHP led
- Can include telephone FU, patient support groups, 1:1 exit interviews
- psychological support, lymphoedema care, psychosocial support, psychosexual support

Address each element on a individual patient basis

The Aims of Follow-Up in Metastatic Breast Cancer are:

- To give continuous psychological support.
- To monitor treatment.
- To prevent complications (e.g. fractures) or to detect them early (e.g. hypercalcaemia).

It is recommended that:

- Patients should be seen at least every three months.
- There should be easy access to the clinic in between visits if necessary.
- It is preferable that the patient sees the same team of doctors regularly.
- Patients should be introduced to appropriate other professionals at an early stage e.g. palliative care team, breast care nurse, physiotherapist, lymphoedema therapist, orthopaedic surgeon.

NICE GUIDELINES FOR PATIENTS WITH A FAMILY HISTORY OF BREAST CANCER

- Each cancer unit should have a specialist breast healthcare professional led breast cancer family history assessment clinic.
- After assessment women will be classified into low risk, moderate risk, or high risk.
- High risk patients will be offered referral to a tertiary centre for genetic assessment.
- Moderate & high risk patients will be screened through NHS BSP units

Management

Moderate and Moderate to High Risk Patients:

- Mammographic surveillance after discussion of risks and benefits (see below)
- Risk management advise for women not suitable for mammography

High Risk Patients:

- Refer to tertiary centre
- Genetic counselling with a view to genetic screening and risk reducing surgery
- Mammographic surveillance (see below)

Mammographic Surveillance

- Not recommended for women under 40 years
- Individual strategies for women aged thirty to thirty-nine years and high risk
- Patients aged forty and over:
 - Aged forty to forty-nine screen yearly
 - Aged fifty and over screen three yearly as part of the NHS Breast Screening Programme
 - MRI and ultrasound should not be used for routine surveillance

Risk Reducing Mastectomy - Family History Patients

These patients have been counselled and have received an estimate of the risk of breast cancer and/or ovarian cancer. They are generally in remission or are well. Advice may include the removal of a normal organ (breast or ovaries) that may potentially be the site of future malignancy, thus reducing the risk of future morbidity or excess mortality. The Geneticist is expected to suggest a timescale for intervention to be successful in reducing the risk of future cancer, typically prophylactic breast surgery in early 30's and oophorectomy in early 40's.

- Patients should have a reasonable risk of a new primary
- Patients should have received genetic counselling
- Patients should be offered a psychological assessment
- A referral to a specialist reconstructive (breast) surgeon should be made and options discussed including mastectomy plus or minus reconstruction, consideration should be given to contralateral reconstruction.
- Referral to a gynaecologist for laproscopic oophorectomy if indicated
- Breast CNS / reconstruction Nurse should be involved

In principle all these components should form part of a planned pathway. Adequate time should be taken at each stage to facilitate decision making. The patient may benefit from future follow up and psychological input as well as management of physical side effects.

Some patients without a proven genetic risk may seek to obtain a prophylactic mastectomy and/or reconstruction and oophorectomy without a proven markedly elevated genetic risk or a moderately elevated risk. This is more difficult to manage. A similar approach is recommended prior to consideration of surgery but with an insistence on psychological assessment and genetic counselling.

A discussion with a colleague for second opinion should be considered.

(Breast Cancer Management Guidelines Christie Breast Disease Group, Section 13, p62 - 64)

Referral criteria to tertiary care (NICE Guideline October 2006)

Female breast cancer

Two 1st or 2nd degree relatives* diagnosed before average age of 50

Three 1st or 2nd degree relatives* diagnosed before average age of 60.

Four relatives* diagnosed at any age.

* at least one must be a 1st degree relative of the consultee

Ovarian cancer

One relative diagnosed with ovarian cancer at any age *plus on the same side of the family there is*

- **One** 1st (including relative with ovarian cancer) or **one** 2nd degree relative diagnosed with breast cancer before age 50
- **One** additional relative diagnosed with ovarian cancer at any age
- **Two** 1st or 2nd degree relative diagnosed with breast cancer before average age of 60

Bilateral breast cancer

One 1st degree relative with cancer diagnosed in both breasts before average age of 50

One 1st or 2nd degree relative diagnosed with bilateral breast cancer *and one* 1st or 2nd degree relative diagnosed with breast cancer before average age of 60

Male breast cancer

One male breast cancer at any age *plus on the same side of the family there is*

- **One** 1st or 2nd degree relative diagnosed with breast cancer before age 50
- **Two** 1st or 2nd degree relative diagnosed with breast cancer before average age of 60

Moderate risk referrals

The Family History Clinic accepts moderate risk referrals from the Manchester Health Authority area which consists of:-

- 1) A single first degree relative under the age of 40.
- 2) 2 relatives under the age of 60 (referees should be a first degree relative of one of these).
- 3) 3 relatives at any age on the same side of the family.

Moderate risk referrals from outside the Manchester Health Authority area may be assessed by the local Breast Unit.

Criteria for genetic testing of relatives

Mutation in BRCA1, BRCA2 or P53 genes detected in family.

- Women with four or more relatives with breast or ovarian cancer on the same side of the family. Blood from a linking affected relative must be obtainable.
- Manchester score of 20+ in an affected family member.
- Ashkenazi Jewish women <60 with one FDR with breast cancer <50 or ovarian cancer at any age.

Proposed criteria for discussing prophylactic surgery

- Lifetime risk of 1 in 4 or more
- Two counselling sessions with geneticist/oncologist
- One or more sessions with psychologist/psychiatrist
- One session with plastic/reconstructive surgeon

Risk-reducing Mastectomy MDT Provision

Patients undergoing risk-reducing mastectomy must be discussed at an MDT where members of the genetic and family history team, psychology team, nursing team and surgical team are present. Current provision of this MDT service is at the Nightingale Centre attended by Prof Evans, Prof Howell, Dr Lalloo, Dr Clancy, Dr Rogers, Dr Maurice, Mr Baildam, Mr Barr, Mr Ross, Mr Wilson, Mrs Potter and Mrs Affen.

Mechanics of referral to the family history clinic

Letter to Prof Gareth Evans or Dr Fiona Lalloo giving as full a family history as possible bearing in mind the criteria for referral.

- Letter will be sent back to you if referral not thought to be appropriate.
- At risk woman sent a family history clinic questionnaire.
- When form returned and clinic appointment is given.
- At visit pedigree checked.
- Subject counselled and offered mammography, genetic testing, prophylactic surgery as appropriate. Entry into clinical trials considered.

13.5.1 Address for referrals

Prof D G R Evans or Dr F Lalloo.
Genetic Medicine,
6th Floor, St Mary's Hospital,
Central Manchester Foundation Trust,
Oxford Road.
Manchester M13 9WL

Prof A Howell or Prof DGR Evans
Family History Clinic
Nightingale Centre & Genesis Prevention Centre,
University Hospital of South Manchester
M23 9LT

SECTION 3: MANAGEMENT OF BENIGN BREAST CONDITIONS

FIBROADENOMA

- Diagnose on double / triple assessment P2 U2 (C2)
- If <2cm it is reasonable to offer an expectant policy, unless patient is keen on having it surgically excised
- It is not necessary to remove benign fibroadenomas
- If the patient with suspected fibroadenoma has had a core biopsy and the result is B2 and has been discussed at the MDTM, the patient can then be safely discharged
- Always advise the patient to re-attend the breast clinic if she perceives an increase in the size of the lesion despite a benign diagnosis of fibroadenoma (C2 / B2)

BREAST PAIN

Breast cancers rarely present with pain alone. Only approximately 5% of breast cancer are associated with pain.

Cyclical Breast Pain:

- Common in premenopausal women
- Pre-menstrual breast pain
- Normal, physiological
- Full assessment and any investigations as per initial assessment protocol, imaging not usually indicated
- Suggest:
 - Reassurance & discharge
 - Supportive bra
 - Drug therapy (Simple analgesia, Danazol, Bromocriptine)

Non-Cyclical Breast Pain:

- Common in older women
- Cyclical breast pain may lose its periodicity and become constant
- May occur in women on HRT
- Can reflect referred pain in chest wall (Tietz syndrome, Osteo-arthritis, Trauma, Other musculo-skeletal conditions)
- Full assessment including mammography in women >40yrs
- Suggest:
 - Reassurance
 - Life style measures
 - Supportive bra
 - Simple analgesia
 - Drug therapy (non-steroidal inflammatory agents)

CYSTS

- New patients of any age presenting with a palpable breast lump – manage with full triple assessment as for any other lump.
- If USS confirms palpable lump to be a cyst, drainage with needle aspiration should be considered
- Cyst fluid does not routinely need to be sent for cytology unless the aspirate is frankly bloody or there is a concern on imaging (U3)
- If cyst has been aspirated clinically (not using image guidance) and a residual lump remains palpable, then re-image to assess this
 - Perform FNA of this residual abnormality
 - If there is no residual abnormality then it is reasonable to reassure and discharge the patient
- If there is no history of forming frequent breast cysts, then patients can be discharged

- If after clinical examination, the surgeon is confident that this is a recurrent breast cyst, it would be reasonable to simply aspirate this without resorting to any imaging. If however there is >12months between the formation of cysts, it may be prudent to have imaging prior to insertion if needle

NIPPLE DISCHARGE

- All patients should have cytology / histology and imaging if discharge is bloody or clear blood stained, and from single duct
- If uniduct and bloody colour discharge, and nipple smear is suspicious:
 - Microdochectomy procedure if single localisable duct
 - Hadfields procedure if duct not localised
- If any other colour:
 - Discharge If nipple smear is normal
 - Microdochectomy procedure if profuse uniduct discharge
- If cytology is indeterminate (C3) microdochectomy / Hadfield's procedure is indicated

GYNAECOMASTIA

- Can occur in males of any age but usually occurs at extremes of life
- History of drug use (Cimetidine, Anabolic Steroids, alcohol, prostate cancer drugs)
- Examine breasts, axillae, supraclavicular area + abdomen, scrotum and testicles
- Clinical exam is usually diagnostic.
- If suspicious FNA will give diagnosis
- Treatment will be reassurance
- Only occasionally is surgery necessary for cosmetic reasons (low clinical priority)

ABSCCESS

- Most breast abscesses do not need emergency drainage. Repeated aspiration and antibiotics should resolve the problem
- Inform patients about repeated aspiration and total time period may exceed 12 weeks
- Ultrasound guidance for needle aspiration will ensure accurate and full drainage
- Aspirate should be sent for culture & sensitivity
- Surgical drainage maybe required for large or multiple abscesses with skin involvement
- Patients with inflammatory mass but consistently no pus should have core biopsy

APPENDIX I

Table I Adjuvant Systemic Treatment: Summary of benefits - Breast Cancer 10 year survival

Risk	NPI ²	Predicted survival, no drug	Polychemotherapy ³ age:			Tam ⁴ [for 5 yr] all ages
			<50	50-59	60-69	
Low						
T1 G1 N0	<2.4	95% ¹	–	–	–	
T1 G1 N1-3 T1 G2 N0 T>1 G1 N0	2.41-3.4	85%	89%	87%	86%	89% ⁴
Intermediate						
T1 G1 N4+ T1 G2 N1-3 T1 G3 N0 T>1 G1 N1-3 T>1 G2 N0	3.41-4.4	70%	78%	74%	72%	78% ⁴
T1 G2 N4+ T1 G3 N1-3 T>1 G1 N4+ T>1 G2 N1-3 T>1 G3 N0	4.41-5.4	50%	64%	57%	54%	63% ⁴
High						
T>1 G2 N4+ T>1 G3 N1-3 TanyG3 N4+	>5.4	20%	42%	31%	26%	41% ⁴
Overall risk reduction			27%	14%	8%	26%

1: Same as age-matched population without breast cancer

2: NPI: Nottingham Prognostic Index: $(0.2 \times \text{size in cm}) + \text{grade (1,2 or 3)} + \text{LN stage}$, where 1=nodes-ve, 2= 1-3 nodes +ve, 3=>4 nodes +ve. T>1 means T 2-7 cm

Example: 1.6 cm Grade 1 tumour node negative. $\text{NPI} = (1.6 \times 0.2) + 1 + 1 = 2.32$

Example: 4.7 cm Grade 3 tumour 6/23 nodes + ve. $\text{NPI} = (4.7 \times 0.2) + 3 + 3 = 6.94$

3: Anthracycline-containing polychemotherapy regimens may confer an increased adjuvant benefit relative to CMF but at the cost of increased morbidity

4: Excluding women with ER poor [~G3] tumours. Also leads to 47% decrease in contralateral tumours. Benefit appears independent of patient age but short-term side effects are more likely the younger the patient. Tamoxifen does not appear to reduce the measured benefit from polychemotherapy, nor does polychemotherapy affect the benefit from Tamoxifen; benefits could therefore be as much as additive when both are used.

T1: 2 cm or less. T2: 2-5 cm T3: > 5 cm T4: any size + skin or chest wall extension

NB; Predictions of outcome using computerised algorithms are widely used and are more current, e.g.

www.adjuvantonline.com

All predictive tables or programs are used in an advisory capacity alone

Appendix 2 Pathology Reports

- Reports should include the following information in order to plan treatments optimally
- Maximum tumour diameter (where assessable).
- Unicentric or Multicentric tumour
- Histological classification of in-situ and invasive tumours
- Histological grade of invasive carcinomas
- Histological grade of DCIS using the NCGBSP recommended method
- Presence or absence of vascular space invasion.
- Completeness of excision with measurement of narrowest margin.
- Total lymph nodes found (when assessable) and total nodes containing metastatic carcinoma in each axillary specimen. Invasion of perinodal fat should be recorded.
- Receptor status (ER, PR, HER 2).

Appendix 3 Radiological Approach To Management Of Breast Cancer

The role of radiology in the management of breast cancer is threefold:-

- Staging
- Assessing disease relapse
- Monitoring of response to therapy

Staging

Prior to definitive treatment patients should have bilateral mammography and chest radiography as a baseline investigation. The indications for any additional radiological investigations are outlined below.

Early Stage [Prior to adjuvant therapy]

- Stage pN0: Not indicated
- Stage pN1: Not routinely indicated, but could be considered for high grade disease, T3 disease or HER-2 over expressing tumours
- Stage pN2: Imaging recommended (CT Chest/Abdomen + Isotope bone scan)
- Stage pN3: Imaging recommended (CT Chest/Abdomen + Isotope bone scan)

Locally advanced disease

- Imaging recommended (CT Chest/Abdomen + Isotope bone scan)

Assessment of locally recurrent disease

In patients with either a clinical or mammographic suspicion of locally recurrent disease in the breast special mammographic views and ultrasound should be performed. Confirmation of recurrence requires needle biopsy for histology or fine needle aspiration cytology. If the results are equivocal MRI may be useful for excluding recurrence. If recurrence is confirmed a chest radiograph, liver ultrasound (or CT Thorax/Abdo) and bone scan should be performed.

Assessment of metastatic (and loco-regionally recurrent) disease

- CT Chest/Abdomen + Isotope bone scan at presentation of metastatic disease [staging scan]
- For patients with visceral disease undergoing chemotherapy
 - Baseline scan [same as staging scan]
 - At half way point through chemotherapy to assess response; assuming that the intention is to give 6 cycles, this means scanning after 9 weeks for 3-weekly cycles. For weekly cycles, imaging after 6-9 weeks is recommended
 - At completion of planned chemotherapy to assess response
- For patients on long term trastuzumab/chemotherapy (e.g. Capecitabine)
 - Baseline scan [same as staging scan]
 - Further scans at 3 monthly intervals to assess response
- For patients with visceral disease undergoing primary hormonal therapy
 - Baseline scan [same as staging scan]
 - After 9-12 weeks of therapy to assess response
 - No further routine CT scans. Rising tumour marker(s) or clinical suspicion of progression to trigger restaging scan
- Other indications
 - CT whole brain for patients with clinical suspicion of cranial metastases
 - Pelvic CT for patients with suspicion of pelvic disease

NOTE: Whilst the recommendation is for CT scanning in this group of patients, clinicians may choose to request US abdomen or plain radiographs instead depending on the clinical scenario and the presence of evaluable lesions on US/plain radiograph.

Radiological Techniques

Mammography:

This is the technique of choice for identifying the primary tumour. As interpretation frequently causes difficulty this examination is usually undertaken in centres where appropriate expertise is available.

Chest radiography:

The chest radiograph is the most common method for evaluating thoracic involvement as it is quick, sensitive, inexpensive and easy to repeat for evaluation of treatment and relapse. PA and lateral views will usually show adenopathy, pulmonary metastases, pleural effusions and advanced bone infiltration. Routine chest radiography is not a cost effective method of monitoring asymptomatic patients for pulmonary metastases and should only be used to address a clinical problem relating specifically to the thorax.

Scintigraphy

Skeletal scintigraphy using 99m-technetium labelled diphosphonate is the examination of first choice for the investigation of symptoms suggestive of bone metastases. As stated previously routine use of bone scintigraphy to detect asymptomatic bone metastases is not indicated.

Ultrasound

Despite its many advantages there is no routine role for ultrasound in staging of asymptomatic patients. In patients with abnormal LFTs it is useful both in confirming the presence of metastases and assessing treatment response. It may also be used in the assessment of pleural effusions.

Computed Tomography (CT)

CT is useful in assessing liver disease in patients who are difficult to examine using ultrasound. It also has a role in the diagnosis of lymphangitis and assessment of intra abdominal disease.

Magnetic Resonance Imaging (MRI)

MRI is the technique of choice to evaluate suspected disease affecting the meninges and spinal cord. MRI is also useful in assessment of the axillae and suspected chest wall invasion. Magnetic resonance mammography (MRM) has role in excluding tumour recurrence within the breast and in assessing response of primary tumour to neo-adjuvant therapy.

PET

¹⁸F-FDG-PET has a potential role in differentiating between benign and malignant breast masses, lymph node staging, detecting metastatic disease, detecting local or distant recurrence and assessing response to treatment because of its increased sensitivity and specificity over the other imaging modalities. PET imaging can be considered to exclude metastatic disease prior to curative surgery when other forms of imaging are equivocal.

Appendix 4 Guide to early recognition and management of spinal cord compression

<p>LOW LEVEL OF CLINICAL SUSPICION</p> <ul style="list-style-type: none"> • Cancer diagnosis • New and persistent, localised back pain • Unilateral nerve root pain (radiates in dermatomal distribution) • Pain on movement • No abnormal neurological signs on examination <p>ACTION NOW:</p> <ul style="list-style-type: none"> • Keep possibility of evolving cord compression in mind. • Arrange investigations as appropriate to deal with pain • Arrange early review of patient by yourself or another professional <p>REASSESS IF SYMPTOMS WORSEN/PROGRESS</p>	<p>HIGH LEVEL OF CLINICAL SUSPICION</p> <ul style="list-style-type: none"> • Cancer diagnosis with documented bone metastases or myeloma • Bilateral nerve root pain especially band-like • Acute escalation of severe spinal pain • Unsteadiness/heaviness in legs • Tingling or electric shocks in spine with a cough or sneeze • Neurological signs may be equivocal <p>ACTION NOW:</p> <ul style="list-style-type: none"> • Urgent referral (same day) to hospital for MRI scan (CT scan if MRI contra-indicated) and urgent treatment if diagnosis confirmed • Start dexamethasone 16 mg daily • Refer to Spinal Cord Compression ICP via Christie Hospital website www.christie.nhs.uk <p>DO NOT DELAY</p>	<p>DEFINITE CLINICAL DIAGNOSIS</p> <p>Unequivocal neurological signs of spinal cord compression</p> <ul style="list-style-type: none"> • Weakness in limbs • Altered sensation with a sensory level • Urinary retention • Upper motor neurone signs or sudden flaccid paralysis • Saddle anaesthesia and sphincter disturbance (cauda equina lesions) <p>ACTION NOW:</p> <ul style="list-style-type: none"> • Discuss with Consultant Oncologist/team (via Christie) if already involved in this patient's care • Urgent referral to hospital * for MRI scan (CT scan if MRI contra-indicated) • Request radiotherapy or surgical decompression as an emergency • *Refer direct to Christie Hospital Consultant if rare tumour (e.g. lymphoma, sarcoma) • Start dexamethasone 16 mg daily • Refer to Spinal Cord Compression ICP via Christie Hospital website www.christie.nhs.uk <p>DO NOT DELAY</p>
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